IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PURDUE PHARMA PRODUCTS L.P., NAPP PHARMACEUTICAL GROUP LTD., BIOVAIL LABORATORIES INTERNATIONAL, SRL, and ORTHO-MCNEIL, INC., Plaintiffs/Counterclaim-defendants, v. PAR PHARMACEUTICAL, INC. and PAR PHARMACEUTICAL COMPANIES, INC., Defendants/Counterclaim-plaintiffs.	C.A. No. 07-255-JJF (CONSOLIDATED)

DECLARATION OF REETA K. WHITNEY IN SUPPORT OF PLAINTIFFS' OPENING BRIEF ON CLAIM CONSTRUCTION

I, Reeta K. Whitney, declare as follows:

1. I am an associate at the firm of Ropes & Gray LLP. I am resident in Ropes & Gray's Palo Alto office, which is located at 525 University Avenue, Palo Alto, California 94301. Ropes & Gray is trial counsel for Plaintiffs Purdue Pharma Products L.P. ("Purdue") and Napp Pharmaceutical Group Ltd. ("Napp") in this action.

2. I make the following declaration in support of Plaintiffs' Opening Brief on Claim Construction.

3. Attached as Exhibit 1 is a true and correct copy of U.S. Patent No. 6,254,887 which has been marked as Defendant's Exhibit 12.

4. Attached as Exhibit 2 is a true and correct copy of U.S. Patent No. 7,074,430 which has been marked as Defendant's Exhibit 19.

5. Attached as Exhibit 3 is an excerpt from DORLAND'S ILLUSTRATED MEDICAL DICTIONARY 1708 (27 Ed. 1988).

6. Attached as Exhibit 4 is an excerpt from the prosecution history file of U.S. Patent No. 7,074,430 which has been marked as Exhibit D93.

I declare under penalty of perjury that the forgoing is true and correct.

Dated: June 13, 2008

REETA K. WHITNEY

CERTIFICATE OF SERVICE

I hereby certify that on June 13, 2008, I caused the foregoing to be electronically filed with the Clerk of the Court using CM/ECF, which will send notification of such filing to:

Frederick L. Cottrell, III, Esquire
Steven J. Fineman, Esquire
RICHARDS, LAYTON & FINGER, P.A.

Richard D. Kirk, Esquire
BAYARD, P.A.

Mary W. Bourke, Esquire
CONNOLLY BOVE LODGE & HUTZ LLP

I further certify that I caused to be served copies of the foregoing document on June 13, 2008, upon the following in the manner indicated:

Frederick L. Cottrell, III, Esquire — *VIA ELECTRONIC MAIL AND HAND DELIVERY*
Steven J. Fineman, Esquire
RICHARDS, LAYTON & FINGER, P.A.
One Rodney Square
Wilmington, DE 19801

Edgar H. Haug, Esquire — *VIA ELECTRONIC MAIL*
Robert E. Colletti, Esquire
FROMMER LAWRENCE & HAUG LLP
745 Fifth Avenue
New York, NY 10151

Richard D. Kirk, Esquire — *VIA ELECTRONIC MAIL AND HAND DELIVERY*
BAYARD, P.A.
222 Delaware Avenue
Suite 900
Wilmington, DE 19801

Mary W. Bourke, Esquire — *VIA ELECTRONIC MAIL AND HAND DELIVERY*
CONNOLLY BOVE LODGE & HUTZ LLP
The Nermours Building
1007 North Orange Street
Wilmington, DE 19801

/s/ Rodger D. Smith II

Rodger D. Smith II (#3778)

EXHIBIT 1

US006254887B1

(12) **United States Patent**
Miller et al.

(10) **Patent No.: US 6,254,887 B1**
(45) **Date of Patent: *Jul. 3, 2001**

(54) **CONTROLLED RELEASE TRAMADOL**

(75) Inventors: **Ronald Brown Miller**, Basel (CH); **Stewart Thomas Leslie**, Cambridge (GB); **Sandra Therese Antoinette Malkowska**, Cambridgeshire (GB); **Kevin John Smith**, Cambridge (GB); **Walter Wimmer**, Limburg (DE); **Horst Winkler**, Linter (DE); **Udo Hahn**, Nentershausen (DE); **Derek Allan Prater**, Cambridge (GB)

(73) Assignee: **Euro-Celtique S.A.**, Luxembourg (LU)

(*) Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **08/677,798**

(22) Filed: **Jul. 10, 1996**

Related U.S. Application Data

(62) Division of application No. 08/241,129, filed on May 10, 1994, now Pat. No. 5,591,452.

(30) **Foreign Application Priority Data**

May 10, 1993	(DE)	43 15 525
Nov. 23, 1993	(GB)	9324045
Mar. 9, 1994	(GB)	9404544
Mar. 14, 1994	(GB)	9404928

(51) **Int. Cl.**[7] **A61K 9/22**

(52) **U.S. Cl.** **424/468**; 424/470; 424/476; 424/480; 424/488; 424/494; 424/495; 424/498; 424/499; 424/502; 514/646

(58) **Field of Search** 424/468, 470, 424/476, 480, 488, 494, 495, 498, 499, 502; 514/646

(56) **References Cited**

U.S. PATENT DOCUMENTS

2,738,303	3/1956	Blythe et al.	167/82
3,065,143	11/1962	Christenson et al.	167/82
3,652,589	3/1972	Flick et al.	260/326.5 M
3,830,934	8/1974	Flick et al.	424/330
3,845,770	11/1974	Theeuwes et al.	128/260
3,950,508	4/1976	Mony et al.	424/19
3,965,256	6/1976	Leslie	424/22
3,974,157	8/1976	Shetty et al.	260/247.2 B
4,013,784	3/1977	Speiser	424/19
4,063,064	12/1977	Saunders et al.	219/121
4,076,798	2/1978	Casey et al.	424/22
4,088,864	5/1978	Theeuwes et al.	219/121
4,132,753	1/1979	Blichare et al.	264/25
4,259,314	3/1981	Lowey	424/19

(List continued on next page.)

FOREIGN PATENT DOCUMENTS

2131350	3/1995	(CA)	A61K/31/135
3602370	8/1987	(DE)	A61K/45/06
3623193	1/1988	(DE)	A61K/31/205
4329794	3/1995	(DE)	A61K/31/135
4329794 A1	3/1995	(DE)	A61K/31/135
0032004	12/1980	(EP)	A61K/9/22
0043254	1/1982	(EP)	A61K/9/26
0097523	8/1983	(EP)	A61K/9/26
0043254	5/1984	(EP)	A61K/9/26
0108218	5/1984	(EP)	A61K/9/22
0108218 A2	5/1984	(EP)	A61K/9/22
0147780	12/1984	(EP)	A61K/9/32
0147780	7/1985	(EP)	A61K/9/32
0152379	8/1985	(EP)	A61K/9/50

(List continued on next page.)

OTHER PUBLICATIONS

Martindale, The Extra Pharmacopoeia, 28th Ed., 1982, 6263–c, Tramadol hydrochloride, pp 1029–1030.

Anderson, H.O. & Christensen, H., *In vitro and in vivo investigations of a new timed–release dosage form of propoxyphene hydrochloride,* Dansk tidsskrift for farmaci, vol. 43, 1969, pp 117–126.

Schmidhammer, Helmut, *Synthesis and Biological Evaluation of 14–Alkoxymorphinans,* Helvetica Chimica Acta, vol. 72, 1989, pp 1233–1239.

Schmidhamer, Helmut, *Synthesis, Structure Elucidation, and Pharmacological Evaluation of 5–Methyl–oxymorphone,* Hevetica Chimica Acta, vol. 71, (1988) pp 1801–1804.

Schmidhammer, Helmut, *Synthesis and Biological Evaluation of 14–Alkoxymorphinans,* J. Med Chem, (1990) vol. 33, No. 4 , pp1200–1206.

ROTE LISTE® Service GmbH, Rote Liste 1998, Section 05.

Stanislaw Janicki and Zdzisiaw Jedras, *Slow–Release Microballs: Method of Preparation,* Acta. Pharm. Technol. 33(3) (1987), pp. 154–155.

B. Elsing and G. Blaschke, *Achiral and chiral high–performance liquid chromatographic determination of tramadol and its major metabolites in urine after oral administration of racemic tramadol,* Journal of Chromatography, 612 (1993), pp. 223–230.

C.H.W. Koks, A.P.E. Vielvoye–Kerkmeer, and J.H. Beijnen, *Tramadol (Tramal),* Pharm. Weekbl. 1993; 128(4): 1298–1300.

W. Lintz and H. Uragg, *Quantitative Determination of Tramadol in Human Serum by Gas Chromatography—Mass Spectrometry,* Journal of Chromatography, 341 (1985), pp. 65–79.

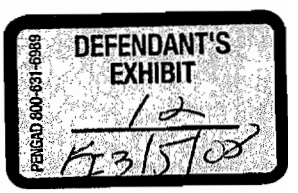
(List continued on next page.)

Primary Examiner—Samuel Barts
(74) *Attorney, Agent, or Firm*—Davidson, Davidson & Kappel, LLC

(57) **ABSTRACT**

A controlled release preparation for oral administration contains tramadol, or a pharmaceutically acceptable salt thereof, as active ingredient.

33 Claims, 1 Drawing Sheet



U.S. PATENT DOCUMENTS

4,343,789	8/1982	Kawata et al.	424/78
4,366,172	12/1982	Lednicer	424/330
4,380,534	4/1983	Fukui et al.	424/38
4,389,393	6/1983	Schor et al.	424/19
4,421,736	12/1983	Walters	424/19
4,483,847	11/1984	Augart	424/22
4,533,562	8/1985	Ikegami et al.	427/3
4,613,619	9/1986	Sleigh et al.	514/546
4,708,874	11/1987	DeHaan et al.	424/470
4,797,410	1/1989	El-Fakahany	514/356
4,801,458	1/1989	Hidaka et al.	424/443
4,801,460	1/1989	Goertz et al.	424/465
4,828,836	5/1989	Elger et al.	424/419
4,834,984 *	5/1989	Goldie et al.	424/488
4,834,985	5/1989	Elger et al.	424/488
4,844,907	7/1989	Elger et al.	424/465
4,844,909	7/1989	Goldie et al.	424/480
4,861,598	8/1989	Oshlack	424/468
4,880,830	11/1989	Rhodes	424/470
4,894,234	1/1990	Sharma et al.	424/440
4,917,899	4/1990	Geoghegan et al.	424/461
4,925,675	5/1990	Giannini et al.	424/469
4,935,246	6/1990	Ahrens	424/490
4,987,136	1/1991	Kreek et al.	514/282
4,990,341	2/1991	Goldie et al.	424/484
5,007,790	4/1991	Shell	424/451
5,023,089	6/1991	Sakamoto et al.	424/502
5,026,560	6/1991	Makino et al.	424/494
5,030,400	7/1991	Danielson et al.	264/101
5,071,646	12/1991	Malkowaka et al.	424/497
5,073,379	12/1991	Klimesch et al.	424/467
5,126,145	6/1992	Evenslad et al.	424/465
5,132,142	7/1992	Jones et al.	427/196
5,133,974	7/1992	Paradissis et al.	424/480
5,162,117	11/1992	Stupak et al.	424/475
5,167,964	12/1992	Muhammad et al.	424/482
5,169,645	12/1992	Shukla et al.	424/499
5,178,868	1/1993	Mamqvist-Granlund et al.	424/490
5,196,203	3/1993	Boehm	424/469
5,202,128	4/1993	Morella et al.	424/469
5,204,119	4/1993	Shiobara et al.	424/489
5,266,331	11/1993	Oshlack et al.	424/468
5,271,934	12/1993	Goldberg et al.	424/401
5,273,760	12/1993	Oshlack et al.	424/480
5,286,493	2/1994	Oshlack et al.	424/468
5,292,461	3/1994	Juch et al.	264/37
5,300,300	4/1994	Egidio et al.	424/456
5,321,012	6/1994	Mayer et al.	514/25
5,330,766	7/1994	Morella et al.	424/490
5,395,626	3/1995	Kotwal et al.	424/472
5,403,593	4/1995	Royce	424/489
5,453,283	9/1995	Münch et al.	424/489
5,468,744 *	11/1995	Raffa et al.	514/282
5,472,710	12/1995	Klekkers-Bethke et al.	424/468
5,521,178	5/1996	Nickel et al.	514/23.2
5,549,912	8/1996	Oshlack	424/468

FOREIGN PATENT DOCUMENTS

0214735	7/1986	(EP)	A61K/9/22
0189861	8/1986	(EP)	A61K/47/00
0248548	5/1987	(EP)	A61K/9/22
0249347	5/1987	(EP)	A61K/31/485
0251459	5/1987	(EP)	A61K/9/22
0253104	6/1987	(EP)	A61K/9/00
0254978	2/1988	(EP)	A61K/9/22
0256127	2/1988	(EP)	C12N/9/00
0256127 B1	2/1988	(EP)	C12N/9/00
0267702	5/1988	(EP)	A61K/9/14
0271193	6/1988	(EP)	A61K/31/485
0271193 A2	6/1988	(EP)	A61K/31/485
0300897	7/1988	(EP)	A61K/9/22
0295212	12/1988	(EP)	A61K/47/00
0327295	8/1989	(EP)	A61K/9/52
0338383	10/1989	(EP)	A61K/9/54
0068450	1/1990	(EP)	A61K/9/20
0351580	1/1990	(EP)	A61K/9/22
0377518	1/1990	(EP)	A61K/9/52
0361680	4/1990	(EP)	A61K/9/46
0361910	4/1990	(EP)	A61K/9/16
0368247	5/1990	(EP)	A61K/9/26
0377517	7/1990	(EP)	A61K/31/52
0377518	7/1990	(EP) .	
0298355	11/1990	(EP)	A61K/9/50
0415693	3/1991	(EP)	A61K/37/02
0430287 B1	6/1991	(EP)	A61K/9/54
0463833	6/1991	(EP)	A61K/9/26
0241615	9/1991	(EP)	A61K/9/22
0452145	10/1991	(EP)	A61K/9/14
0531611	4/1992	(EP)	A61K/9/02
0535841	9/1992	(EP)	A61K/31/485
0526862	2/1993	(EP)	A61K/9/20
0533297	3/1993	(EP)	A61K/9/16
0534628	3/1993	(EP)	A61K/31/485
0546676	6/1993	(EP)	A61K/31/60
0595311	5/1994	(EP)	A61K/31/44
0361910	6/1994	(EP)	A61K/9/16
0636370	2/1995	(EP)	A61K/31/485
0642788	3/1995	(EP)	A61K/31/135
0609961	8/1995	(EP)	A61K/31/485
0205282	9/1995	(EP)	A61K/9/22
0624366	5/1996	(EP)	A61K/31/135
2642420	3/1990	(FR)	C07C/55/10
997399	4/1964	(GB) .	
1405088	6/1971	(GB)	A61K/9/26
1513166	6/1978	(GB)	B29B/1/02
2111386	12/1982	(GB)	A61K/9/20
2117239	3/1983	(GB)	A61K/9/20
2053681	4/1984	(GB)	A61K/9/22
2196848	5/1988	(GB)	A61K/9/22
2246514	2/1992	(GB)	A61K/9/16
2287880	10/1995	(GB)	A61K/9/14
54-92631	7/1979	(JP) .	
4217925	8/1992	(JP) .	
2568202	12/1996	(JP)	A61K/31/485
WO9119484	12/1991	(WO)	A61K/9/16
WO9119485	12/1991	(WO)	A61K/9/16
WO9201446	2/1992	(WO)	A61K/9/50
WO9202209	2/1992	(WO)	A61K/9/22
WO9205774	4/1992	(WO)	A61K/9/18
WO9206679	4/1992	(WO)	A61K/9/16
WO9300076	1/1993	(WO)	A61K/9/51
WO9304675	3/1993	(WO)	A61K/31/16
WO9307859	4/1993	(WO)	A61K/9/16
WO9307861	4/1993	(WO)	A61K/9/50
WO9317667	9/1993	(WO)	A61K/9/16
WO9318753	9/1993	(WO)	A61K/9/16
WO9324110	12/1993	(WO)	A61K/9/20
WO9403160	2/1994	(WO)	A61K/9/32
WO9403161	2/1994	(WO)	A61K/9/52
WO9405262	3/1994	(WO)	A61K/9/16
WO9422431	10/1994	(WO)	A61K/9/20
WO9423700	10/1994	(WO)	A61K/9/16
WO9514460	6/1995	(WO)	A61K/9/14

OTHER PUBLICATIONS

Pharm. Res. 1992; Supp. 9:308, *Tramadol*, PPDM's 8207 and 8206.

W. Lintz, H. Barth, G. Osterloh, and E. Schmid–Bothelt, *Bioavailability of Enteral Tramadol Formulations 1st Communication: Capsules,* Arzeimittel–Forschung, Drug Res. 36 (II) Nr. 8 (1986), pp. 1278–1283.

Jean–Marie Besson and Michael D. Vickers, *Tramadol Analgesia Synergy in Research and Therapy,* Drugs 47 (Suppl. 1):1–2, 1994, Adis International Limited.

Pierre Dayer, Laurence Collart and Jules Desmeules, *The Pharmacology of Tramadol,* Drugs 47 (Suppl. 1):3–7, 1994, Adis International Limited.

Abraham Sunshine, *New Clinical Experience with Tramadol,* Drugs 47 (Supp. 1) 8–18, 1994, Adis International Limited.

Klaus A. Lehmann, *Tramadol for the Management of Acute Pain,* Drugs 47 (Supp. 1):19–32, 1994, Adis International Limited.

Keith Budd, *Chronic Pain—Challenge and Response,* Drugs 47 (Suppl. 1):39–43, 1994, Adis International Limited.

Jordi Cami, Xavier Lamas and Magi Farre, *Acute Effects of Tramadol in Methadone–Maintained Volunteers,* Drugs 47 (Supp. 1):39–43, 1994, Adis International Limited.

C. Rhoda Lee, Donna Mc Tavish and Eugene M. Surkin, "Tramadol, A Preliminary Review of its Pharmacodynamic Properties, and Therapeutic Potential in Acute and Chronic Pain States", Drugs 46(2):313–340, 1993, Adis International Limited.

Valerie Kayser, Jean–Marie Beeson, and Gisele Gilbaud, *Evidence for a noradrenergic component in the antinociceptive effect of the analgesic agent tramadol in an animal model of clinical pain, the arthritic rat,* European Journal of Pharmacology, 224 (1992), pp. 83–88.

Kenzie L. Preston, Donald R. Jasinksi and Margaret Testa, *Abuse potential and pharmacological comparison of tramadol and morphine,* Drug and Alcohol Dependence, 27 (1991), pp. 7–17.

Valerie Kayser, Jean–Marie Beeson and Gisele Guilbaud, *Effects of the analgesic agent tramadol in normal and arthritic rats: comparison with the effects of different opioids, including and cross–tolerance to morphine,* European Journal of Pharmacology, 195 (1991) 37–45.

T. Murano, H. Yamamoto, N. Endo, Y. Kudo, N. Okada, Y. Masuda, and I. Yano, *Studies of Dependence on Tramadol in Rats,* Arzneimittel–Forschung, Drug Res. 28(I) Heft 1a (1978).

T. Yanagita, *Drug Dependence Potential of 1–(m–Methoxyphenil)–2–(dimethylaminomethyl)–cyclohesan–1–ol Hydrochloride (Tramadol) Tested in Monkeys,* Arzneimittel–Forschung Drug Res. 28(I), Heft 1a (1978), pp. 158–163.

Abraham Sunshine, MD, Nancy Z. Olson, MPS, Itic Zighelboim, MD, Ana DeCastro, RN, and Frederick L. Minn, MD, PhD, *Analgesic oral efficacy of tramadol hydrochloride in postoperative pain,* Clin. Pharmacol. Ter. (Jun. 1992), pp. 740–146.

Translation of Japanese Patent Publication No. 43 (1968) 20006, Detailed Description of the Invention.

M. Ahmend and R.P. Enever, *Formulation and Evaluation of Sustained Release Paracetamol Tablets,* Journal of Clinical and Hospital Pharmacy (1981) 6, pp. 27–38.

M.D. Vickers, D. O'Flaherty, S.M. Szekely, M. Read and J. Yoshizumi, *Tramadol: pain relief by an opioid without depression of respiration,* Anaesthesia, 1992, vol. 47, pp. 291–296.

G.M. Hanna, C.A. Lau–Cam and W.M. Plank, *Direct determination of the enantiomeric purity of tramadol hydrochloride by proton nuclear resonance (1H NMR spectroscopy with chiral lanthanide shifr reacgent,* Pharmazie 44 (1989), H 5, pp. 321–325.

S.J. Carter and R. Woodford, "Long–Acting Oral Medicaments", Pharmacy Digest (1961) pp. 183–189.

Remington's Pharmaceutical Sciences, 1980, p. 1598.

Thomsen, L. Juul, et al., *Prolonged Release Matrix Pellets Prepared by Melt Pelletization II. Hydrophobic Substances as Meltable Binders,* Drug Development and Industrial Pharmacy, vol. 20, No. 7, (1984), pp. 1179–1197.

Von K. Fliek, E. Frankus and E. Friderichs—Tramadol, 107–113, *Untersuchungen zur chemlschen Strukhur und analgeslachen Wirkung von phenylsubstituterien Aminomethylgycolohexanglen,* Arzneimittel–Forschung, Drug Res. 28 (1), Heft 1a, and English translation.

Kuschinsky et al., *Kurges Lehrbuch der Pharmakologie und Toxikologic,* Georg Theimo Verlag Stuttgart, New York 1987, p270–273.

Von E. Frankus, II. Friderichs, S.M. Kin und G. Osterioh, *Uber die Isomerentronnung, Strukuraufklarung und pharmakologische Charaklerisierung von 1–(m–Methoxyphenyl)–2–(dimethylaminomethyl)–cyclohexand–1–ol,* Arzneim–Forsch, Drug Res. (I), Heft la (1978), 144–121 and English translation.

Rote Liste 1992, Entry No. 05020.

Derwent WPI C92–138727 Abstract JP 04/217 925 of 07.08.92.

Herbert P. Fledler: Loxicon der Hilfastoffe, 34d Ed., 1989, p272–273.

Sueker et al., (Eds.), Pharmazeutische Technologie, Stuttgart 1979, p497–498.

Von W. Vogel, H. Burchardi, K. Sibler und L. Valic, *Über die Wirkung von Tramadol auf Almung und Kreislauf,* Arzneimittel–Forschung, Drug. Res. 28(I), Heft 1a (1978), pp. 183–186 and English translation.

Von W. Lintz, S. Erlacin, E. Frankus and H. Uragg, *Metabolismus von Tramadol bol Mensch and Tier,* Arzneimittel–Forschung, Drug Res. 31 (II), Nr. 11 (1981), pp. 1932–1943 and English translation.

Von F. Lagler, F. Helm, V. Etzol und H. Kiel, *Toxikologisache Untersuchungen mit Tramadol. einem neuen Analgelikum,* Arzneimittel–Forschung, Drug Res. 28(I), Heft 1a (1978), pp. 164–172 and English translation.

Von G. Osterloh, E. Friderichs*, F. Felgenheuer*, W.A. Gunzler, Z. Henmi**, T. Kitano**, M. Nakamura**, H. Hayashi** und I. Ishii**, *Allgemeine pharmakologische Unternuchungen mit Tramadol einem stark wirkenden Analgenikum,* Arzneimittel–Forschung, Drug Res. 28(I), Heft 1a (1978) pp. 135–151 and English translation.

Von E. Friderichs, F. Felgenhauer, P. Jongschaap und G. Osterloh, *Pharmakologische Untersuchungen zur Analgesic, Abhangigheim–und Toleranzentwicklung–von Tramadol. einem stark wirkenden Analgetikum,* Arzneimittel–Forschung Drug Res. 28(I), Heft 1a, pp. 122–134 and English translation.

L. Collart, C. Luthy, C. Favario–Constantin, P. Dayer, *Dualite de l'effel analgesique du tramadol chez l'homme,* Schwiz Med. Wochenschr. 1993: 123: pp. 2241–2243 and English translation.

E. Beubler, *Medikamenlose Schmerzhergnie: Krieterien, Müglichkelten, Risken,* Therapiewoche Österreich 7,2 (1992), pp. 90–96 and English translation.

Kaiko, et al., *A Single–dose Study of the Effect of Food Ingestion and Timing of Dose Administration on the Pharmacokinetic Profile of 30mg* Sustained–release Morphine Sulfate Tablets, Current Therapeutic Research, pp. 869–878, vol. 47, No. 5, May 1990.

Kaiko, et al., *Controlled–release Morphine Bioavailability (MS Contin™ Tablets) in the Presence and Absence of Food,* The Hospice Journal, pp. 17–30, vol. 6(4) 1990.

Gourlay, et al., *The Reproducibility of Bioavailability of Oral Morphine from Solution under Fed and Fasted Conditions,* Journal of Pain and Symptom Management, vol. 6, No. 7, Oct. 1991, pp. 431–436.

Gourlay, et al., *Influence of a High–fat Meal on the Absorption of Morphine from Oral Solutions,* Clin. Pharmacol. Ther., Oct. 1989, pp. 403–468.

Physicians Desk Reference 1994, 48th Edition, pp. 1821–1824.

Advertisement: Roxanol SR., 1988 Roxane Labs, Inc.

R. Kaiko and T. Hunt, *Comparison of the Pharmacokineric Profiles of Two Oral Controlled–Release Morphine Formulations in Healthy Young Adults,* Clin. Thera., vol. 13, No. 4, 1991, pp. 484–488.

Thomsen, L. Juul, *Prolonged Release Matrix Pellets Prepared by Melt Pelletization, Part IV: Drug Content, Drug Particle Size, and Binder Composition,* Pharmaceutical Technology Europa. (Oct. 1994), pp. 19–22.

McTaggart, C.M., et al., *The Evaluation of Formulation and Processing Conditions of a Melt Granulation Process,* Int. J. Pharm., vol. 19, No. 2, issued 198, pp. 139–148.

El–Shanawany, S., *Sustained Release of Nitrofurantoin Front Inert Wax Matrixes,* J. Controlled Release, vol. 26, No. 1, issued 1993, pp. 11–19.

S. Bloomfield, et al., *Analgesic Efficacy and Potency of Two Oral Controlled–Release Morphine Preparations,* Clin. Pharmacol. Ther., vol. 53, No. 4, 1993, pp. 469–478.

Advertisement MS Contin™ 1986, 1987 The Purdue Frederick Company.

P. Flanders, et al., *The Control of Drug Releases From Conventional Melt Granulation Matrices,* Drug Development and Industrial Pharmacy, vol. 13, No. 6, (1987), pp. 1001–1022.

T. Schaefer, et al., *Melt granulation in a laboratory scale high shear mixer,* Drug Development and Industrial Pharmacy, vol. 16, No. 8, (1990), pp. 1249–1277.

Thompson, L. Junl et al., Schaefer, T., et al., *Prolonged Release Matrix Pellets Prepared by Melt Pelletization, I. Process Variables,* Drug Development and Industrial Pharmacy, vol. 19, No. 15, pp. 1867–1887.

Thomsen, L. Juul, et al., *Prolonged Release Matrix Pellets Prepared by Melt Pelletization, Part IV, Drug Content, Drug Particle Size, and Binder Composition,* Pharmaceutical Technology Europe, (Oct. 1994), pp. 19–24.

Thomsen, L. Juul, *Utilizing melt pelletization technique for the preparation of prolonged release products, Pelletization,* (material elaborated by Assistant Prof. Lars Juul Thomsen, Dept. of Pharmaceutics, Royal Danish School of Pharmacy for the DIE course "Pelletization Technology", Nov. 1992, Sections I to VI.

SK Baveja et al., Int. J. Pharmaceutics, 41, (1988) p55–62.

Formulating for Controlled Release with METHOCEL® Premium Cellulose Ethers. The Dow Chemical Company, 1989.

M S Vasquez et al., Drug Dev. & Ind. Pharmacy, 18 (11 & 12), p1355–1378 (1992).

L W S Cheong et al, Pharm. Res 9(11) p1510–151 (1992).

Pharmazeutische Stoffiste 6th Ed., 1985 p. 196.

Rote Liste 1993 Nos. 05001 & 05008.

Derwent Abstract 92:64751 1985.

Haltbarkeim–Herstellungsdalen deutscher Arzneimittel p486 1985.

Goodman and Gilmans, 8th Ed., 1990:p497.

Hunt, et al., Clin. Ther. vol. 13, No. 4, 1991, pp. 482–488.

Lee et al. Drugs 46(2), 1993, pp. 313–340.

The Merck Index 11th Ed., 1989.

Pharmazeulische Stoffiate 10, Auflage, p. 193, 11/94.

Rote Liste 1992 Entry 05007.

PIL (Product Information Leaflet) about MST CONTINUS® tablets.

Graph of dissolution rates claimed in the patent EP 0 624 366.

The Physician's Desk Reference, 1994. Monograph on MS CONTIN® (MST CONTINUS®) tablets.

DA Aldermann, Int. J. Pharm. Tech. and Prod. Mfr., 5(3) p1–9, 1984.

HE Huber et al., J. Pharm. Sci. 55 (9) Sep. 1966, p974–976.

Lin SY et al., Current Therapeutic Research 52 (3), p. 486–492, Sep., 1992.

Handbook of Pharmaceutical Excipients, p138–140, 1986.

Aqualon Technical Information Bulletin VC–585, 1991.

P Colombo, Advanced Drug Delivery Reviews, 11 (1993) p37–57.

KV Ranga Rao et al., Int. J. Pharmaceutics, 48 (1988) p1–13.

JE Hogan, Drug Dev. & Ind. Pharmacy, 15 (6 & 7), p975–999 (1989).

JL Ford et al., Int. J. Pharmaceutics, 24 (1985) p327–338.

PB Daly et al. Int. J. Pharmaceutics, 18 (1984) p201–205.

H. Lapidus et al., J. Pharm. Sci., 55(8), Aug. 1966, p840–843.

H Lapidus et al., J. Pharm. Sci., 57(8), Aug. 1968, p1292–1301.

Abstract of JP 54/092631, published Jul. 23, 1979.

J.M. Aiache and J. Hirtz, *Biopharmaceutics—Absolute Bioavailability of Tramal Suppositories,* Third European Congress of Biopharmaceutics and Pharmacokinetics Proceedings—vol. 1, p. 311, 1992.

Clinical Pharm. & Ther. vol. 53, No. 2, *American Society for Clinical Pharmacology and Therapeutics,* P111–67, P111–68 and P111–69, 1993.

* cited by examiner

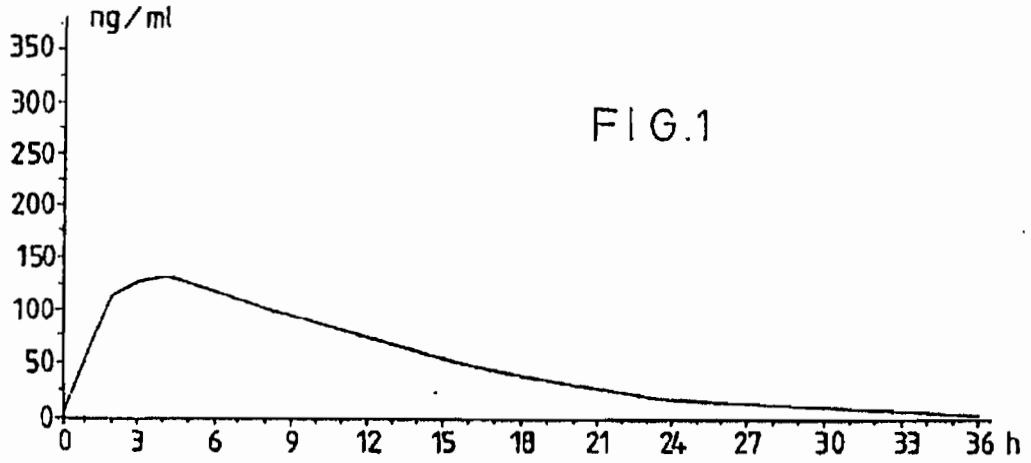

ng/ml
350
300
250
200
150
100
50
0
0
3
6
9
12
15
18
21
24
27
30
33
36 h

FIG.1

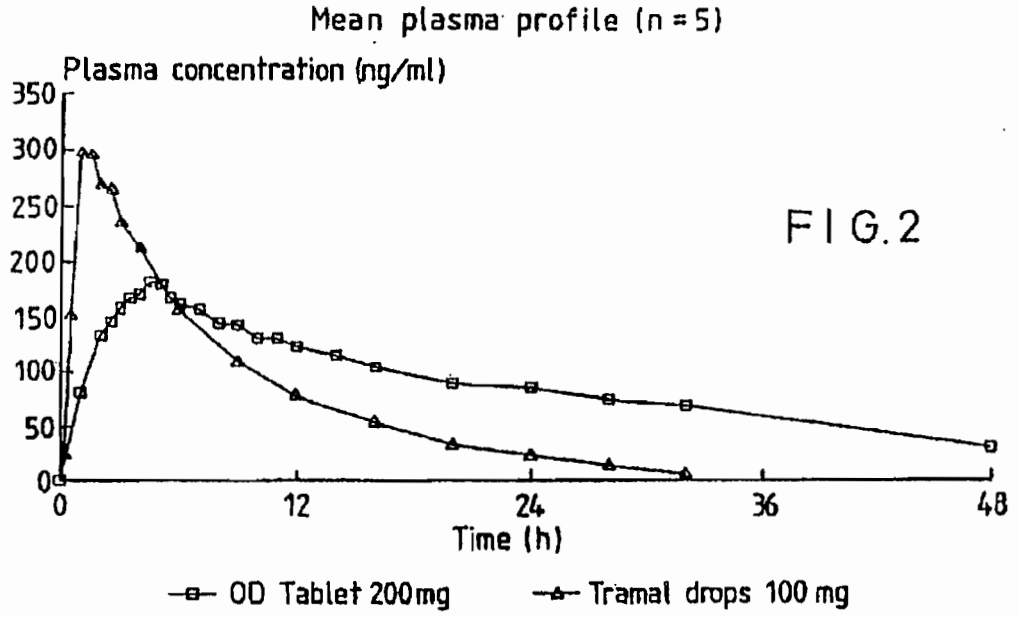

Mean plasma profile (n = 5)
Plasma concentration (ng/ml)
350
300
250
200
150
100
50
0
0
12
24
36
48
Time (h)
OD Tablet 200mg
Tramal drops 100 mg

FIG.2

CONTROLLED RELEASE TRAMADOL

This is a divisional of application Ser. No. 08/241,129, filed May 10, 1994 (now U.S. Pat. No. 5,591,452).

The present invention relates to a controlled release preparation for oral administration, to processes for its preparation and to its medical use. In particular, (lie invention relates to a controlled release preparation comprising tramadol or a pharmaceutically acceptable salt thereof.

Tramadol, which has the chemical name (+)-trans-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol, is an orally active opioid analgesic. Conventional release preparations in the form of capsules, drops and suppositories containing tramadol, or more particularly its hydrochloride salt, have been commercially available for many years for use in the treatment of moderate to severe pain; Such preparations, however, do not provide a controlled release of the tramadol. Moreover, despite tramadol's long-standing use, controlled release preparations for oral administration containing tramadol as active ingredient have not even previously been described in the literature.

It is an object of the present invention to provide an oral controlled release tramadol preparation suitable for at least twelve-hourly (e.g. up to twenty-four hourly) administration for the treatment of pain.

The present invention therefore provides a controlled release preparation comprising tramadol or a pharmaceutically acceptable salt thereof for oral administration.

Suitable pharmaceutically acceptable salts of tramadol for use according to the present invention are those conventionally known in the art such as pharmaceutically acceptable acid addition salts. The hydrochloride salt is particularly preferred.

A controlled release preparation according to the present invention is one that achieves slow release of a drug over an extended period of time, thereby extending the duration of drug action over that achieved by conventional delivery. Preferably such a preparation maintains a drug concentration in the blood within the therapeutic range for 12 hours or more.

The present inventors have found that in order to allow for controlled release tramadol over at least a twelve hour period following oral administration, the in vitro release rate preferably corresponds to the following % rate of tramadol released:

TABLE 1

TIME (H)	% RELEASED
1	0–50
2	0–75
4	3–95
8	10–100
12	20–100
16	30–100
24	50–100
36	>80

Another preferred preparation especially suited for twice-a-day dosing has an in vitro release rate corresponding to the following % rate of tramadol released:

TABLE 2

TIME (H)	% RELEASED
1	20–50
2	40–75

TABLE 2-continued

TIME (H)	% RELEASED
4	60–95
8	80–100
12	90–100

Yet another preferred preparation particularly suited for once-a-day dosing has an in-vitro release rate corresponding to the following % rate of tramadol released:

TABLE 3

TIME (H)	% RELEASED
1	0–50
2	0–75
4	10–95
8	35–100
12	55–100
16	70–100
24	>90

A still further preferred preparation in accordance with the invention also particularly suited for once-a-day dosing has an in vitro release rate corresponding to the following % rate if tramadol released.

TABLE 4

TIME (H)	% RELEASED
1	0–30
2	0–40
4	3–55
8	10–65
12	20–75
16	30–88
24	50–100
36	>80

More preferably a preparation for once-a-day dosing has an in vitro release rate substantially as follows:

TIME (H)	% TRAMADOL RELEASED
1	15–25
2	25–35
4	30–45
8	40–60
12	55–70
16	60–75

Another preferred dissolution rate in vitro upon release of the controlled release preparation for administration twice daily according to the invention, is between 5 and 50% (by weight) tramadol released after 1 hour, between 10 and 75% (by weight) tramadol released after 2 hours, between 20 and 95% (by weight) tramadol released after 4 hours, between 40 and 100% (by weight) tramadol released after 8 hours, more than 50% (by weight) tramadol released after 12 hours, more than 70% (by weight) released after 18 hours and more than 80% (by weight) tramadol released after 24 hours.

Furthermore, it is preferred in the case of a controlled release preparation for administration twice daily that after 8 hours following oral administration between 70 and 95% (by weight) tramadol is absorbed in vivo, between 77 and 97% (by weight) tramadol is absorbed after 10 hours and between 80 and 100% (by weight) tramadol is absorbed after 12 hours.

A formulation in accordance with the invention suitable for twice-a-day dosing may have a tmax of 1.5 to 8 hours, preferably 2 to 7 hours, and a W_{50} value in the range 7 to 16 hours.

A formulation in accordance with the invention suitable for once-a-day dosing may have a tmax in the range of 3 to 6 hours, preferably 4 to 5 hours and a W_{50} value in the range of 10 to 33 hours.

The W_{50} parameter defines the width of the plasma profile at 50% Cmax, i.e. the duration over which the plasma concentrations are equal to or greater than 50% of the peak concentration. The parameter is determined by linear interpolation of the observed data and represents the difference in time between the first (or only) upslope crossing the last (or only) downslope crossing in the plasma profile.

The in vitro release rates mentioned herein are, except where otherwise specified, those obtained by measurement using the Ph. Eur. Paddle Method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37° C. and using UV detection at 270 mm.

The in vitro absorption rate is determined from measurement of plasma concentration against time using the deconvolution technique. A conventional release tramadol drop preparation (Tramal (trade mark), Grunenthal) was used as the weighting-function and the elimination half life of tramadol was taken as 7.8 hours.

Tie controlled release preparation according to the invention preferably contains an analgesically effective amount of tramadol or a pharmaceutically acceptable salt thereof, conveniently in the range of from 50 to 800 mg, especially 100, 200, 300, 400 to 600 mg (calculated as tramadol hydrochloride) per dosage unit.

The controlled release preparation according to the invention may be presented, for example, as granules, spheroids, pellets, multiparticulates, capsules, tablets, sachets, controlled release suspensions, or in any other suitable dosage form incorporating such granules, spheroids, pellets or multiparticulates.

The active ingredient in the preparation according to the invention may suitably be incorporated in a matrix. This may be any matrix that affords controlled release tramadol over at least a twelve hour period and preferably that affords in-vitro dissolution rates and in vivo absorption rates of tramadol within the ranges specified above. Preferably the matrix is a controlled release matrix. Alternatively, normal release matrices having a coating which provides for controlled release of the active ingredient may be used.

Suitable materials for inclusion in a controlled release matrix include

(a) Hydrophillic or hydrophobic polymers, such as gums, cellulose ethers, acrylic resins and protein derived materials. Of these polymers, the cellulose ethers, especially alkylcelluloses are preferred. The preparation may conveniently contain between 1% and 80% (by weight) of one or more hydrophillic or hydrophobic polymers.

(b) Digestible, long chain (C_8–C_{50}, especially C_{12}–C_{40}), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils and waxes, hydrocarbons having a melting point of between 25 and 90° C. are preferred. Of these long chain hydrocarbon materials, fatty (aliphatic) alcohols are preferred. The preparation may conveniently contain up to 60% (by weight) of at least one digestible, long chain hydrocarbon.

(c) Polyalkylene glycols. The preparation may suitably contain up to 60% (by weight) of one or more polyalkylene glycols.

One particularly suitable controlled release matrix comprises one or more alkylcelluloses and one or more C_{12}–C_{36} aliphatic alcohols. The alkylcellulose is preferably C_1–C_6 alkyl cellulose, especially ethyl cellulose. The controlled release preparation according to the invention preferably contains from 1 to 20% (by weight), especially from 2 to 15% (by weight) of one or more alkylcelluloses.

The aliphatic alcohol may conveniently be lauryl alcohol, myristyl alcohol or stearyl alcohol but is preferably cetyl alcohol or more preferably cetostearyl alcohol. The controlled release preparation suitably contains from 5 to 30% (by weight) of aliphatic alcohol, especially from 10 to 25% (by weight) of aliphatic alcohol.

Optionally the controlled release matrix may also contain other pharmaceutically acceptable ingredients which are conventional in the pharmaceutical art such as diluents, lubricants, binders, granulating aids, colourants, flavourants, surfactants, pH adjusters, anti-adherents and glidants, e.g. dibutyl sebacate, ammonium hydroxide, oleic acid and colloidal silica.

The controlled release preparation according to the invention may conveniently be film coated using any film coating material conventional in the pharmaceutical art. Preferably an aqueous film coating is used.

Alternatively, the controlled release preparation according to the invention may comprise a normal release matrix having a controlled release coating. Preferably the preparation comprises film coated spheroids containing the active ingredient and a spheronising agent.

The spheronising agent may be any suitable pharmaceutically acceptable material which may be spheronised together with the active ingredient to form spheroids. A preferred spheronising agent is microcrystalline cellulose. The microcrystalline cellulose used may suitably be, for example, Avicel PH 101 or Avicel PH 102 (Trade Marks, FMC Corporation).

Optionally the spheroids may contain other pharmaceutically acceptable ingredients conventional in the pharmaceutical art such as binders, bulking agents and colourants. Suitable binders include water soluble polymers, water soluble hydroxyalkyl celluloses such as hydroxypropylcellulose or water insoluble polymers (which may also contribute controlled release properties) such as acrylic polymers or copolymers for example ethylcellulose. Suitable bulking agents include lactose.

The spheroids are coated with a material which permits release of the active ingredient at a controlled rate in an aqueous medium. Suitable controlled release coating materials include water insoluble waxes and polymers such as polymethylacrylates (for example Eudragit polymers, Trade Mark) or water insoluble celluloses, particularly ethylcellulose. Optionally, water soluble polymers such as polyvinylpyrrolidone or water soluble celluloses such as hydroxypropylmethylcellulose or hydroxypropylcellulose may be included. Optionally other water soluble agents such as polysorbate 80 may be added.

Alternatively the drug may be coated onto inert nonpareil beads and the drug loaded beads coated with a material which permits control of the release of the active ingredient into the aqueous medium.

In a further aspect the present invention provides a process for preparing a controlled release preparation according to the present invention comprising incorporating tramadol or a pharmaceutically acceptable salt thereof in a controlled release matrix, for example by

(a) granulating a mixture comprising tramadol or a pharmaceutically acceptable salt thereof and one or more alkylcelluloses,

(b) mixing the alkylcellulose containing granules with one or more C_{12-36} aliphatic alcohols; and optionally

(c) shaping and compressing the granules, and film coating, if desired; or

(d) granulating a mixture comprising tramadol or a pharmaceutically acceptable salt thereof, lactose and one or more alkylcelluloses with one or more C_{12-36} aliphatic alcohol; and, optionally,

(e) shaping and compressing the granules, and film coating, if desired.

The controlled release preparation according to the invention may also be prepared in the form of film coated spheroids by

(a) granulating the mixture comprising tramadol or a pharmaceutically acceptable salt thereof and a spheronising agent;

(b) extruding the granulated mixture to give an extrudate;

(c) spheronising the extrudate until spheroids are formed; and

(d) coating the spheroids with a film coat.

One preferred form of unit dose form in accordance with the invention comprises a capsule filled with controlled release particles essentially comprising the active ingredient, a hydrophobic fusible carrier or diluent and optionally a hydrophillic release modifier. In particular, the controlled release particles are preferably prepared by a process which comprises forming a mixture of dry active ingredient and fusible release control materials followed by mechanically working the mixture in a high speed mixer with an energy input sufficient to melt or soften the fusible material whereby it forms particles with the active ingredient. The resultant particles, alter cooling, are suitably sieved to give particles having a size range from 0.1 to 3.0 mm, preferably 0.25 to 2.0 mm. An example according to the invention is described below which is suitable for the commercial production of dosage units.

When using such a processing technique it has been found that, in order most readily to achieve the desired release characteristics (both in vivo and in vitro as discussed above) the composition to be processed should comprises two essential ingredients namely:

(a) tramadol or salt thereof; and

(b) hydrophobic fusible carrier or diluent; optionally together with

(c) a release control component comprising a water-soluble fusible material or a particulate soluble or insoluble organic or inorganic material.

We have found that the total amount of tramadol or pharmaceutically acceptable salt thereof in the composition may vary within wide limits, for example from 10 to 90% by weight thereof.

The hydrophobic fusible component (b) should be a hydrophobic material such as a natural or synthetic wax or oil, for example hydrogenated vegetable oil, hydrogenated castor oil, microcrystalline wax, Beeswax, Carnauba wax or glyceryl monostearate, and suitably has a melting point of from 35 to 140° C., preferably 45 to 110° C.

The release modifying component (c), when a water soluble fusible material, is conveniently a polyethylene glycol and, when a particulate material, is conveniently a pharmaceutically acceptable material such as dicalcium phosphate or lactose.

Another preferred process for the manufacture of a formulation in accordance with the invention comprises

(a) mechanically working in a high-speed mixer, a mixture of tramadol or a pharmaceutically acceptable salt in particulate form and a particulate, hydrophobic fusible carrier or diluent having a melting point from 35 to 140° C. and optionally a release control component comprising a water soluble fusible material, or a particulate soluble or insoluble organic or inorganic material at a speed and energy input which allows the carrier or diluent to melt or soften, whereby it forms agglomerates,

(b) breaking down the larger agglomerates to give controlled release seeds; and

(c) continuing mechanically working with optionally a further addition of low percentage of the carrier or diluent.

(d) optionally repeating steps (c) and possibly (b) one or more times.

This process is capable of giving a high yield (over 80%) of particles in a desired size range, with a desired uniformity of release rate of tramadol or salt thereof.

The resulting particles may be sieved to eliminate any over-or undersized material then formed into the desired dosage units by for example, encapsulation into hard gelatin capsules containing the required dose of the active substance or by compression into tablets.

In this method in accordance with the invention preferably all the tramadol or salt thereof is added in step (a) together with a major portion of the hydrophobic fusible release control material used. Preferably the amount of fusible release control material added in step (a) is between 10% and 90% w/w of the total amount of ingredients added in the entire manufacturing operation, more preferably between 20% and 70% w/w.

Stage (a) of the process may be carried out in conventional high speed mixers with a standard stainless steel interior, e.g. a Collette Vactron 75 or equivalent mixer. The mixture is processed until a bed temperature about 40° C. or above is achieved and the resulting mixture acquires a cohesive granular texture, with particle sizes ranging from about 1–3 mm to fine powder in the case of non-aggregated original material. Such material, in the case of the embodiments described below, has the appearance of agglomerates which upon cooling below 40° C. have structural integrity and resistance to crushing between the fingers. At this stage the agglomerates are of an irregular size, shape and appearance.

The agglomerates are preferably allowed to cool. The temperature to which it cools is not critical and a temperature in the range room temperature to 37° C. may be conveniently used.

The agglomerates are broken down by any suitable means, which will comminute oversize agglomerates and produce a mixture of powder and small particles preferably with a diameter under 2 mm. It is currently preferred to carry out the classification using a Jackson Crockatt granulator using a suitable sized mesh, or a Comil with an appropriate sized screen. We have found that if too small a mesh size is used in the aforementioned apparatus the agglomerates melting under the action of the beater or impeller will clog the mesh and prevent further throughput of mixture, thus reducing yield. A mesh size of 12 has been found adequate.

The classified material is returned to the high speed mixer and processing continued.

It is believed that this leads to cementation of the finer particles into particles of uniform size range.

In one preferred form of the method of the invention processing of the classified materials is continued, until the hydrophobic fusible materials used begin to soften/melt and optionally additional hydrophobic fusible material is then added. Mixing is continued until the mixture has been transformed into particles of the desired predetermined size range.

In order to ensure uniform energy input into the ingredients in the high speed mixer it is preferred to supply at least part of the energy by means of microwave energy.

Energy may also be delivered through oiler means such as by a heating jacket or via the mixer impeller and chopper blades.

After the particles have been formed they are cooled or allowed to cool, and may then be sieved to remove any over or undersized material.

The resulting particles may be used to prepare dosage units in accordance with the invention in the form of e.g. tablets or capsules in manners known per se.

We have also found that particles containing tramadol or a salt thereof produced by a melt processing as described in application PCT/SE93/00225 and the process described and claimed in our prior unpublished UK application No. 9324045.5 filed onNov. 23, 1993 as well as the process described herein are particularly useful for processing into the form of tablets.

We have found that by suitable selection of the materials used in forming the particles and in the tabletting and the proportions in which they are used, enables a significant degree of control in the ultimate dissolution and release rates of the tramadol or salt thereof from the compressed tablets.

Usually, to form a tablet in accordance with the invention, particles prepared as described above will be admixed with tabletting excipients e.g. one or more of the standard excipients such as diluents, lubricants, binding agents, flow aids, disintegrating agents, surface active agents or water soluble polymeric materials.

Suitable diluents are e.g. microcrystalline cellulose, lactose and dicalcium phosphate. Suitable lubricants are e.g. magnesium stearate and sodium stearyl fumarate. Suitable binding agents are e.g. hydroxypropyl methyl cellulose, polyvidone and methyl cellulose.

Suitable disintegrating agents are starch, sodium starch glycolate, crospovidone and croscarmalose sodium.

Suitable surface active are Poloxamer 188®, polysorbate 80 and sodium lauryl sulfate. Suitable flow aids are talc colloidal anhydrous silica. Suitable water soluble polymers are PEG with molecular weights in the range 1000 to 6000.

To produce tablets in accordance with the invention, particles produced in accordance with the invention may be mixed or blended with the desired excipient(s), if any, using conventional procedures, e.g. using a Y-Cone or bin-blender and the resulting mixture compressed according to conventional tabletting procedure using a suitable size tabletting mould. Tablets can be produced using conventional tabletting machines, and in the embodiments described below were produced on standard single punch F3 Manesty machine or Kilian RLE15 rotary tablet machine.

Generally speaking we find that even with such a highly water soluble active agent as tramadol or salt thereof tablets formed by compression according to standard methods give very low release rates of the active ingredient e.g. corresponding to release over a period of greater than 24 hours, say more than 36. We have found that the release profile can be adjusted in a number of ways. For instance a higher loading of the drug will be associated with increased release rates; the use of larger proportions of the water soluble fusible material in the particles or surface active agent in the tabletting formulation will also be associated with a higher release rate of the active ingredient. By controlling the relative amounts of these ingredients it is possible to adjust the release profile of the tramadol or salt thereof.

In order that the invention may be well understood the following examples are given by way of illustration only.

BRIEF DESCRIPTION OF DRAWINGS

The present invention is further illustrated in connection with the accompanying drawings in which:

FIG. 1 is a graphical depiction of the serum levels of tramadol following administration of one tablet according to Example 2 in 12 healthy volunteers: and

FIG. 2 is a graphical depiction of the plasma profile resulting from single dose administration of the tablet of Example 8 in comparison to the administration of a commercial preparation of tramadol drops 100 mg in a trial involving five healthy male volunteers.

EXAMPLE 1

Tablets having the following formulation wee prepared:

	mg/tablet
Tramadol Hydrochloride	100
Lactose Ph. Eur.	68.0
Ethylcellulose (Surelease ® 25% solids)	15
Purified Water Ph. Eur.	13.3*
Cetostearyl Alcohol Ph. Eur. (Dehydag wax 0)	42.00
Magnesium Stearate Ph. Eur.	2.00
Purified Talc Ph. Eur.	3.00
	230.00

*Removed during processing.

Tramadol hydrochloride (100 mg) and lactose (68 mg) were granulated, transferred to a fluid bed granulator and sprayed with ethylcellulose (15 mg) and water. The granules were then dried at 60° C. and passed through a 1 mm screen.

To the warmed tramadol containing granules was added molten cetostearyl alcohol (42 mg) and the whole was mixed thoroughly. The granules were allowed to cool and sieved through a 1.6 mm screen. Purified talc and magnesium stearate were added and mixed with the granules. The granules were then compressed into tablets.

The tablets were coated with a film coat having the formulation given below.

	mg/tablet
Hydropopylmethylcellulose Ph. Eur. 15 cps (Methocel E15)	0.770
Hydroxypropylmethylcellulose (Ph. Eur. 5 cps (Methocel E5)	3.87
Opaspray M-1-7111B (33% solids)	2.57
Polyethylene glycol 400 USNF	0.520
Purified Talc Ph. Eur.	0.270
Purified Water Ph. Eur.	55.52*

*Remove during processing.

EXAMPLE 2

Tablets having the following formulation were prepared:

	mg/tablet
Tramadol hydrochloride	100.0
Lactose Ph. Eur.	58.0
Ethylcellulose USNF	15.0

-continued

	mg/tablet
(Ethocel 45 CP)	
Cetostearyl alcohol Ph. Eur.	52.0
(Dehydag wax O)	
Magnesium stearate Ph. Eur.	2.00
Purified talc Ph. Eur.	3.00

A mixture of tramadol hydrochloride (100 mg), lactose (58 mg) and ethylcellulose (15 mg) was granulated whilst adding molten cetostearyl alcohol (52 mg) and the whole was mixed thoroughly. The granules were allowed to cool and sieved through a 1.6 mm screen. Purified talc and magnesium stearate were added and mixed with the granules. The granules were then compressed into tablets which were coated with a film coat having the formulation given in Example 1.

EXAMPLE 3

Film coated tablets were produced following the procedure described in Example 2 and having the following formulation:

	mg/tablet
Tramadol hydrochloride	100.00
Lactose Ph. Eur.	70.50
Hydroxyethylcellulose Ph. Eur.	12.50
Cetostearyl alcohol Ph. Eur.	42.00
Magnesium stearate Ph. Eur.	2.00
Purified talc Ph. Eur.	3.00

In vitro dissolution studies

In vitro dissolution studies were conducted on tablets prepared as described above. Results are given in Table 1.

TABLE 1

	WT % TRAMADOL RELEASED		
Time (h)	Example 1	Example 2*	Example 3
1	39	35	43
2	52	47	60
4	67	62	84
8	82	78	97
12	90	86	—

*Measured on tablet core

In a trial involving 12 healthy volunteers the serum levels of tramadol following administration of one tablet according to Example 2 was found to be as illustrated in FIG. 1.

EXAMPLES 4 AND 5

Particles having the formulations given in Table II below were prepared by the steps of:

i. Placing the ingredients (a) and (c) (total batch weight 0.7 kg) in the bowl of a 10 liter capacity Collette Gral Mixer (or equivalent) equipped with variable speed mixing and granulating blades;

ii. Mixing the ingredients at about 150–1000 rpm whilst applying heat until the contents of the bowl are agglomerated.

iii. Classifying the agglomerated material by passage through a Comil and/or Jackson Crockatt to obtain controlled release seeds.

iv. Warming and mixing the classified material in the bowl of a 10 liter Collette Gral, until uniform multiparticulates of the desired pre-determined size range are formed in yield of greater than 80%. This takes approximately 5 minutes.

v. Discharging the multiparticulates from the mixer and sieving them to separate out the multiparticulates collected between 0.5 and 2 mm aperture sieves.

TABLE II

Example	4	5
(a) Tramadol HCl (Wt %)	50	75
(b) Hydrogenated Vegetable Oil (Wt %)	50	25

EXAMPLE 6

Samples of the particles from Example 4 were blended with magnesium stearate and purified talc using a Y-Cone or bin-blender. The blended mixture was then compressed using either (1) 14×6 mm, (2) 16×7 mm or (3) 18.6×7.5 mm capsule shaped tooling on a single punch F3 Manesty tabletting machine to give tablets giving 200, 300 and 400 mg of tramadol HCl. The ingredients per dosage unit amounted to the following:

TABLE III

TABLET	MG/TABLET		
INGREDIENT	1	2	3
Tramadol Hcl	200	300	400
Hydrogenated Vegetable Oil	200	300	400
Sub Total	400	600	800
Purified Talc	12.63	18.95	25.26
Magnesium Stearate	8.42	12.63	16.84

The tablets were assessed by the dissolution using Ph. Eur. Paddle Method 100 rpm, 0.1 N HCl.

To assess the non-compressed particles the Ph Eur. Paddle was replaced by a modified Ph Eur. Basket.

The results are shown in Table IV below;

TABLE IV

HOURS AFTER START OF TEST	Particles	Tablet 1	Tablet 2	Tablet 3
	% TRAMADOL HCl RELEASED			
1	54	16	15	15
2	68	23	20	21
3	76	28	25	25
4	82	32	28	28
6	89	40	35	35
8	93	46	41	40
10	96	50	45	45
12	98	55	49	49
16	100	63	57	56
20	NR	70	63	NR

These results confirm the effectiveness of the tabletting in reducing the release rate.

EXAMPLE 7

Samples of the particles from Example 5 were then tabletted using a procedure similar and the ingredients per unit dosage amounted to:

TABLE V

TABLET	MG/TABLET		
INGREDIENT	4	5	6
Tramadol Hcl	200	360	400
Hydrogenated Vegetable Oil	66.7	100	133
Sub Total	266.7	400	533
Purified Talc	7.63	11.44	15.25
Magnesium Stearate	5.16	7.63	10.17

The tablets and samples of non-compressed multiparticulates (each sample containing 400 mg of tramadol hydrochloride) were assessed by the dissolution method also described above. The results are shown in Table VI below;

TABLE VI

HOURS AFTER START OF TEST	Particles	Tablet 4	Tablet 5	Tablet 6
	% TRAMADOL HCl RELEASED			
1	77	43	40	42
2	92	64	55	56
3	98	75	65	66
4	100	83	72	73
6	102	94	83	84
8	102	100	91	91
10	102	NR	96	97

These results show that by increasing the loading of the highly water soluble tramadol hydrochloride (75% w/w in this example compared with 50% w/w in Example 6) a significantly faster release rate of the active ingredient can be achieved.

EXAMPLE 8

Example 4 was repeated but with (lie following formulation:

Tramadol HCl	200 mg/tablet
Hydrogenated Vegetable Oil	163.0 mg/tablet

The resulting multiparticulates were blended as described in Example 6 with the following;

Purified Talc	11.5 mg/tablet
Magnesium Stearate	7.66 mg/tablet

The blend was then compressed as described in Example 6 but using 15 mm×6.5 mm normal concave capsule shaped plain/plain punches.

The resulting tablets were then assessed by the dissolution method described above. The results are shown in Table V.

HOURS AFTER START OF TEST	% TRAMADOL HCl RELEASED
1	20
2	27
3	32
4	37
6	44
8	50

-continued

HOURS AFTER START OF TEST	% TRAMADOL HCl RELEASED
10	55
12	60
16	67
20	73
24	77

In a trial involving five healthy male volunteers the plasma profile resulting from single dose administrations of the above tablet are shown in FIG. 2 in comparison to the administration of a commercial preparation of Tramadol drops 100 mg.

What is claimed is:

1. A controlled release oral pharmaceutical preparation suitable for dosing every 24 hours comprising

a substrate comprising a pharmaceutically effective amount of tramadol or a salt thereof;

said substrate coated with a controlled release coating;

said preparation having a dissolution rate in vitro when measured using the Ph. Eur. Paddle Method at 100 rpm in 900 ml 0,1 N hydrochloric acid at 37° C. and using UV detection at 270 nm, between 0 and 50% tramadol released after 1 hour; between 0 and 75% tramadol released after 2 hours; between 3 and 95% tramadol released after 4 hours; between 10 and 100% tramadol released after 8 hours; between 20 and 100% tramadol released after 12 hours; between 30 and 100% tramadol released after 16 hours; between 50 and 100% tramadol released after 24 hours; and greater than 80% tramadol released after 36 hours, by weight, said preparation providing a therapeutic effect for about 24 hours after oral administration.

2. A controlled release preparation as claimed in claim 1, having an in vitro dissolution rate (measured by the Ph. Eur. Paddle method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37° C. And using UV detection at 270 mm) as set forth below:

TIME (H)	% RELEASED
1	20–50
2	40–75
4	60–95
8	80–100
12	90–100.

3. A controlled release preparation as claimed as claim 1, having an in vitro dissolution rate (measured by the Ph. Eur. Paddle method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37° C. and using UV detection at 270 mm) as set forth below:

TIME (H)	% RELEASED
1	0–50
2	0–75
4	10–95
8	35–100
12	55–100
16	70–100
24	>90.

4. A controlled release preparation as claimed in claim 1, having an in vitro dissolution rate (measured by the Ph. Eur.

Paddle method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37° C. and using UV detection at 270 mm) as set forth below:

TIME (H)	% RELEASED
1	0–30
2	0–45
4	3–55
8	10–65
12	20–75
16	30–88
24	50–100
36	>80.

5. A controlled release preparation according to claim 1, wherein said substrate comprises a plurality of spheroids.

6. A controlled release preparation according to claim 5, wherein said spheroids comprise a spheronizing agent.

7. A controlled release preparation suitable for dosing every twelve hours comprising

a substrate comprising an effective amount of tramadol or pharmaceutically acceptable salt thereof and said substrate coated wit a controlled release coating;

said preparation exhibiting an in vitro dissolution rate when measured by the Ph. Eur. Paddle method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37° C. and using UV detection at 270 mm, such that between 5 and 50% (by weight) tramadol is released after 1 hour, between 10 and 75% by weight) tramadol is released after 2 hours, between 20 and 95% (by weight) tramadol is released after 4 hours, between 40 and 100% (by weight) tramadol is released after 8 hours, more than 50% (by weight) tramadol is released after 12 hours, more than 70% (by weight) tramadol is released after 18 hours and more than 80% (by weight) tramadol is released after 24 hours said preparation providing a therapeutic effect for at least about 12 hours after oral administration.

8. A controlled release preparation according to claim 7, wherein said substrate comprises a plurality of spheroids.

9. A controlled release preparation according to claim 7 which provides a t_{max} at 2 to 7 hours after oral administration.

10. A controlled release preparation according to claim 7, which provides a t_{max} at 1.5 to 8 hours after oral administration.

11. A controlled release preparation according to claim 7, which provides a W_{50} from about 7 to about 16 hours after oral administration.

12. A controlled release preparation according to claim 7, wherein said substrate is a tablet.

13. A controlled release oral pharmaceutical tablet suitable for dosing every 24 hours comprising

a tablet containing a pharmaceutically effective amount of tramadol or a salt thereof;

said tablet coated with a controlled release coating;

said coated tablet having a dissolution rate in vitro when measured using the Ph. Eur. Paddle Method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37° C. and using UV detection at 270 nm, between 0 and 50% tramadol released after 1 hour; between 0 and 75% tramadol released after 2 hours; between 3 and 95% tramadol released after 4 hours; between 10 and 100% tramadol released after 8 hours; between 20 and 100% tramadol released after 12 hours; between 30 and 100% tramadol released after 16 hours; between 50 and 100% tramadol released after 24 hours; and greater than 80% tramadol released after 36 hours, by weight, and providing a W_{50} in the range of 10 to 33 hours when orally administered, said coated tablet providing a therapeutic effect for about 24 hours after oral administration.

14. A controlled release oral pharmaceutical tablet suitable for dosing every 24 hours comprising

a tablet containing a pharmaceutically effective amount of tramadol or a salt thereof;

said tablet coated with a controlled release coating;

said coated tablet providing a therapeutic effect for about 24 hours after oral administration and having an in vitro dissolution rate (measured by the Ph. Eur. Paddle method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37° C. and using UV detection at 270 mm) as set forth below:

TIME (H)	% RELEASED
1	20–50
2	40–75
4	60–95
8	80–100
12	90–100.

15. A controlled release oral pharmaceutical tablet in accordance with claim 15 which has

an in vitro dissolution rate (measured by the Ph. Eur. Paddle method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37° C. using UV detection at 27 mm) as set forth below:

TIME (H)	% RELEASED
1	0–50
2	0–75
4	10–95
8	35–100
12	55–100
16	70–100
24	>90.

16. A controlled release preparation according to claim 1, which when orally administered provides a W_{50} value in the range of 10 to 33 hours.

17. A controlled release preparation according to claim 1, having an in vitro dissolution rate (measured by the Ph. Eur. Paddle method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37° C. and using UV detection at 270 mm) as set forth below:

TIME (H)	% RELEASED
1	15–25
2	25–35
4	30–45
8	40–60
12	55–70
16	60–75.

18. A controlled release preparation according to claim 1, which when orally administered provides a t_{max} at 4–5 hours after oral administration.

19. A controlled release oral pharmaceutical preparation suitable for dosing every 24 hours comprising

a substrate comprising a pharmaceutically effective amount of an opioid analgesic consisting essentially of tramadol or a salt thereof;

said substrate coated with a controlled release coating;

said preparation having a dissolution rate in vitro when measured using the Ph. Eur. Paddle Method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37° C. and using UV detection at 270 nm, between 0 and 50% tramadol released after 1 hour; between 0 and 75% tramadol released after 2 hours; between 3 and 95% tramadol released after 4 hours; between 10 and 100% tramadol released after 8 hours; between 20 and 100% tramadol released after 12 hours; between 30 and 100% tramadol released after 16 hours; between 50 and 100% tramadol released after 24 hours; and greater than 80% tramadol released after 36 hours, by weight, said preparation providing a therapeutic effect for about 24 hour, after oral administration.

20. A controlled release preparation according to claim **1**, wherein said substrate comprises inert non-pareil beads coated with said tramadol.

21. A controlled release preparation according to claim **7**, wherein said substrate comprises inert nonpareil beads coated with said tramadol.

22. A controlled release preparation according to claim **19**, wherein said substrate comprises inert non-pareil beads coated with said tramadol.

23. A controlled release preparation according to claim **19**, wherein said substrate is a tablet.

24. A controlled release preparation according to claim **19**, wherein said substrate comprises spheroids.

25. A controlled release preparation according to claim **19**, which provides a t_{max} from 3 to 6 hours after orally administered to a human patient,

26. A controlled release preparation according to claim **25**, which provides a W_{50} value in the range from 10 to 33 hours.

27. A controlled release preparation in accordance with claim **1**, wherein said controlled release coating comprises a material selected from the group consisting of a water insoluble wax, a water insoluble polymer, a water insoluble cellulose and mixtures of any of the foregoing.

28. A controlled release preparation in accordance with claim **7**, wherein said controlled release coating comprises a material selected from the group consisting of a water insoluble wax, a water insoluble polymer, a water insoluble cellulose and mixtures of any of the foregoing.

29. A controlled release preparation in accordance with claim **13**, wherein said controlled release coating comprises a material selected from the group consisting of a water insoluble wax, a water insoluble polymer, a water insoluble cellulose and mixtures of any of the foregoing.

30. A controlled release preparation in accordance with claim **14**, wherein said controlled release coating comprises a material selected tom the group consisting of a water insoluble wax, a water insoluble polymer, a water insoluble cellulose and mixtures of any of the foregoing.

31. A controlled release preparation in accordance with claim **19**, wherein said controlled release coating comprises a material selected from the group consisting of a water insoluble wax, a water insoluble polymer, a water insoluble cellulose and mixtures of any of the foregoing.

32. A controlled release preparation in accordance with claim **26**, wherein said controlled release coating comprises a material selected from the group consisting of a water insoluble wax, a water insoluble polymer, a water insoluble cellulose and mixtures of any of the foregoing.

33. A controlled release preparation in accordance with claim **11**, wherein said controlled release coating comprises a material selected from the group consisting of a water insoluble wax, a water insoluble polymer, a water insoluble cellulose and mixtures of any of the foregoing.

* * * * *

EXHIBIT 2

US007074430B2

(12) **United States Patent**
Miller et al.

(10) **Patent No.: US 7,074,430 B2**
(45) **Date of Patent: *Jul. 11, 2006**

(54) **CONTROLLED RELEASE TRAMADOL TRAMADOL FORMULATION**

(75) Inventors: **Ronald Brown Miller**, Basel (CH); **Sandra Therese Antoinette Malkowska**, Cambridgeshire (GB); **Walter Wimmer**, Limburg (DE); **Udo Hahn**, Nentershausen (DE); **Stewart Thomas Leslie**, Cambridge (GB); **Kevin John Smith**, Cambridge (GB); **Horst Winkler**, Linter (DE); **Derek Allan Prater**, Cambridge (GB)

(73) Assignee: **Euro-Celtique S.A.**, Luxembourg (LU)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/800,204**

(22) Filed: **Mar. 6, 2001**

(65) **Prior Publication Data**

US 2001/0036477 A1 Nov. 1, 2001

Related U.S. Application Data

(63) Continuation of application No. 08/677,798, filed on Jul. 10, 1996, now Pat. No. 6,254,887, which is a continuation of application No. 08/241,129, filed on May 10, 1994, now Pat. No. 5,591,452.

(51) **Int. Cl.**
A61K 9/22 (2006.01)

(52) **U.S. Cl.** **424/468**; 424/470; 424/480; 424/488; 424/494; 424/495; 424/499; 424/502; 424/424; 514/646

(58) **Field of Classification Search** 424/468, 424/470, 476, 480, 488, 444, 445, 498, 499, 424/502; 514/646
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

2,738,303	A	3/1956	Blythe et al.	167/82
3,065,143	A	11/1962	Christenson et al.	167/82
3,652,589	A	3/1972	Flick et al.	260/326.5 M
3,830,934	A	8/1974	Flick et al.	424/330
3,845,770	A	11/1974	Theeuwes et al.	128/260
3,950,508	A	4/1976	Mony et al.	424/19
3,965,256	A	6/1976	Leslie	424/22
3,974,157	A	8/1976	Shetty et al.	260/247.2 B
4,013,784	A	3/1977	Speiser	424/19
4,063,064	A	12/1977	Saunders et al.	219/121
4,076,798	A	2/1978	Casey et al.	424/22
4,088,864	A	5/1978	Theeuwes et al.	219/121
4,132,753	A	1/1979	Blichare et al.	264/25
4,259,314	A	3/1981	Lowey	424/19
4,343,789	A	8/1982	Kawata et al.	424/78
4,366,172	A	12/1982	Lednicer	424/330
4,380,534	A	4/1983	Fukui et al.	424/38
4,389,393	A	6/1983	Schor et al.	424/19
4,421,736	A	12/1983	Walters	424/19
4,483,847	A	11/1984	Augart	424/22
4,533,562	A	8/1985	Ikegami et al.	427/3
4,613,619	A	9/1986	Sleigh et al.	514/546
4,708,874	A	11/1987	De Haan et al.	424/470
4,797,410	A	1/1989	El-Fakahany	514/356
4,801,458	A	1/1989	Hidaka et al.	424/443
4,801,460	A	1/1989	Goertz et al.	424/465
4,828,836	A	5/1989	Elger et al.	424/419
4,834,984	A	5/1989	Goldie et al.	424/465
4,834,985	A	5/1989	Elger et al.	424/488
4,844,907	A	7/1989	Elger et al.	424/465
4,844,909	A	7/1989	Goldie et al.	424/480
4,861,598	A	8/1989	Oshlack	424/468
4,880,830	A	11/1989	Rhodes	424/470
4,894,234	A	1/1990	Sharma et al.	424/440
4,917,899	A	4/1990	Geoghegan et al.	424/461
4,925,675	A	5/1990	Giannini et al.	424/469
4,935,246	A	6/1990	Ahrens	424/490
4,987,136	A	1/1991	Kreek et al.	514/282
4,990,341	A	2/1991	Goldie et al.	424/484
5,007,790	A	4/1991	Shell	424/451
5,023,089	A	6/1991	Sakamoto et al.	424/502
5,026,560	A	6/1991	Makino et al.	424/494
5,030,400	A	7/1991	Danielsen et al.	264/101
5,071,646	A	12/1991	Malkowska et al.	424/497
5,073,379	A	12/1991	Klimesch et al.	424/467
5,126,145	A	6/1992	Evenstad et al.	424/465
5,132,142	A	7/1992	Jones et al.	427/196
5,133,974	A	7/1992	Paradissis et al.	424/480
5,162,117	A	11/1992	Stupak et al.	424/475
5,167,964	A	12/1992	Muhammad et al.	424/482
5,169,645	A	12/1992	Shukla et al.	424/499
5,178,868	A	1/1993	Malmqvist-Granlund et al.	424/490
5,196,203	A	3/1993	Boehm	424/469
5,202,128	A	4/1993	Morella et al.	424/469

(Continued)

FOREIGN PATENT DOCUMENTS

CA	2131350	3/1995	

(Continued)

OTHER PUBLICATIONS

CAPLUS Online Printout of Raffa et al (Caplus 1992: 120745, J. Pharmacol. Exp. Ther. 1992, 260 (1), 275-85).*

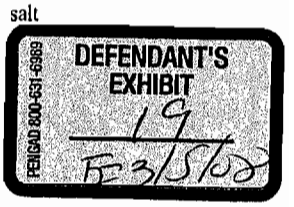
(Continued)

Primary Examiner—Samuel Barts
(74) *Attorney, Agent, or Firm*—Davidson, Davidson & Kappel, LLC

(57) **ABSTRACT**

A controlled release preparation for oral administration contains tramadol, or a pharmaceutically acceptable salt thereof, as active ingredient.

17 Claims, 2 Drawing Sheets



U.S. PATENT DOCUMENTS

5,204,119	A	4/1993	Shiobara et al.	424/489
5,266,331	A	11/1993	Oshlack et al.	424/468
5,271,934	A	12/1993	Goldberg et al.	424/401
5,273,760	A	12/1993	Oshlack et al.	424/480
5,286,493	A	2/1994	Oshlack et al.	424/468
5,292,461	A	3/1994	Juch et al.	264/37
5,300,300	A	4/1994	Egidio et al.	424/456
5,321,012	A	6/1994	Mayer et al.	514/25
5,330,766	A	7/1994	Morella et al.	424/490
5,395,626	A	3/1995	Kotwal et al.	424/472
5,403,593	A	4/1995	Royce	424/489
5,453,283	A	9/1995	Münch et al.	424/489
5,456,921	A	10/1995	Mateescu et al.	
5,468,744	A	11/1995	Raffa et al.	514/282
5,472,710	A	12/1995	Klokkers-Bethke et al.	424/468
5,472,712	A	12/1995	Oshlack et al.	424/480
5,478,577	A	12/1995	Sackler et al.	424/489
5,521,178	A	5/1996	Nickel et al.	514/23.2
5,549,912	A	8/1996	Oshlack et al.	424/468
5,580,578	A	12/1996	Oshlack et al.	424/468
5,591,452	A *	1/1997	Miller et al.	424/468
5,603,956	A	2/1997	Mateescu et al.	
5,616,343	A	4/1997	Cartilier et al.	
5,639,476	A	6/1997	Oshlack et al.	424/468
5,849,240	A	12/1998	Miller et al.	264/460
5,885,615	A	3/1999	Chouinard et al.	
5,891,471	A	4/1999	Miller et al.	424/468
5,958,452	A	9/1999	Oshlack et al.	424/457
5,958,459	A	9/1999	Chasin et al.	424/490
5,965,161	A	10/1999	Oshlack et al.	424/457
5,965,163	A	10/1999	Miller et al.	424/468
5,968,551	A	10/1999	Oshlack et al.	424/456
6,068,855	A	5/2000	Leslie et al.	424/468
6,103,261	A	8/2000	Chasin et al.	424/459
6,143,322	A	11/2000	Sackler et al.	424/459
6,143,353	A	11/2000	Oshlack et al.	427/221
6,162,467	A	12/2000	Miller et al.	424/468
6,254,887	B1 *	7/2001	Miller et al.	424/468
6,261,599	B1	7/2001	Oshlack et al.	424/457
6,294,195	B1	9/2001	Oshlack et al.	424/457
6,306,438	B1	10/2001	Oshlack et al.	424/468
6,326,027	B1	12/2001	Miller et al.	424/468
6,335,033	B1	1/2002	Oshlack et al.	424/457
6,338,859	B1	1/2002	Leroux et al.	
6,399,096	B1	6/2002	Miller et al.	424/464
6,419,957	B1	7/2002	Lenaerts et al.	
6,607,748	B1	8/2003	Lenaerts et al.	
6,645,527	B1	11/2003	Oshlack et al.	424/468
6,743,442	B1	6/2004	Oshlack et al.	424/456
2003/0124184	A1	7/2003	Mezaache et al.	424/465

FOREIGN PATENT DOCUMENTS

DE	3602370	8/1987
DE	3623193	1/1988
DE	4329794	3/1995
DE	4329794 A1	3/1995
EP	0032004	12/1980
EP	0043254	1/1982
EP	0097523	8/1983
EP	0043254	5/1984
EP	0108218	5/1984
EP	0108218 A2	5/1984
EP	0147780	12/1984
EP	0147780	7/1985
EP	0152379	8/1985
EP	0214735	7/1986
EP	0189861	8/1986
EP	0248548	5/1987
EP	0249347	5/1987
EP	0251459	5/1987
EP	0253104	6/1987
EP	0254978	2/1988
EP	0256127	2/1988
EP	0256127 B1	2/1988
EP	0267702	5/1988
EP	0271193	6/1988
EP	0271193 A2	6/1988
EP	0300897	7/1988
EP	0295212	12/1988
EP	0327295	8/1989
EP	0338383	10/1989
EP	0068450	1/1990
EP	0351580	1/1990
EP	0377518	1/1990
EP	0361680	4/1990
EP	0361910	4/1990
EP	0368247	5/1990
EP	0377517	7/1990
EP	0377518	7/1990
EP	0298355	11/1990
EP	0415693	3/1991
EP	0430287 B1	6/1991
EP	0463833	6/1991
EP	0241615	9/1991
EP	0452145	10/1991
EP	0531611	4/1992
EP	0535841	9/1992
EP	0526862	2/1993
EP	0533297	3/1993
EP	0534628	3/1993
EP	0546676	6/1993
EP	0595311	5/1994
EP	0361910	6/1994
EP	0636370	2/1995
EP	0642788	3/1995
EP	0609961	8/1995
EP	0205282	9/1995
EP	0624366	5/1996
FR	2642420	3/1990
GB	997399	4/1964
GB	1405088	6/1971
GB	1513166	6/1978
GB	2111386	12/1982
GB	2117239	3/1983
GB	2053681	4/1984
GB	2196848	5/1988
GB	2246514	2/1992
GB	2287880	10/1995
JP	5492631	7/1979
JP	4217925	8/1992
JP	2568202	12/1996
WO	WO 9119484	12/1991
WO	WO 9119485	12/1991
WO	9201446	2/1992
WO	WO 9201446	2/1992
WO	WO 9202209	2/1992
WO	WO 9205774	4/1992
WO	WO 9206679	4/1992
WO	WO 9300076	1/1993
WO	WO 9304675	3/1993
WO	WO 9307859	4/1993
WO	WO 9307861	4/1993
WO	WO 9317667	9/1993
WO	WO 9318753	9/1993
WO	WO 9324110	12/1993
WO	WO 9403160	2/1994
WO	WO 9403161	2/1994
WO	WO 9405262	3/1994
WO	WO 9422431	10/1994
WO	WO 9423700	10/1994
WO	WO 9514460	6/1995
WO	03072025	9/2003
WO	03072089	9/2003
WO	04000197	12/2003

WO 04080447 9/2004

OTHER PUBLICATIONS

Von K. Flick, E. Frankus and E. Friderichs—Tramadol, 107-113, *Untersuchungen zur chemischen Struktur und analgetischen Wirkung von phenylsubstituierten Aminomethylcyclohexanolen*, Arzneimittel-Forschung, Drug Res. 28 (I), Heft 1a, and English translation.

Kuschinsky et al., *Kurzes Lehrbuch der Pharmakologie end Toxikologie*, Georg Theime Verlag Stuttgart, New York 1987, p. 270-273.

Von E. Frankus, E. Friderichs, S.M. Kin und G. Osterioh, *Über die Isomerentrennung, Strukturaufklärung und pharmakologische Charakterisierung von 1-(m-Methoxyphenyl)-2-(dimethylaminomethyl)-cyclohexan-1-ol*, Arzneim-Forsch. Drug Res. (I), Heft 1a (1978), 144-121 and English translation.

Rote Liste 1992, Entry No. 05020.

Derwent WPI C92-138727 Abstract JP 04/217 925 of Aug. 7, 1992.

Herbert P Fiedler: Lexicon der Hilfsstoffe, 34d Ed., 1989, p. 272-273.

Sucker et al., (Eds.), Pharmazeutische Technologie, Stuttgart, 1979, p. 497-498.

Von W. Vogel, H. Burchardi, K. Sihler und L. Valic, *Über die Wirkung von Tramadol auf Atmung und Kreislauf*, Arzneimittel-Forschung, Drug. Res. 28(1), Heft 1a (1978), pp. 183-186 and English translation.

Von W. Lintz, S. Erlacin, E. Frankus and H. Uragg, *Metabolismus von Tramadol bei Mensch and Tier*, Arzneimittel-Forschung, Drug Res. 31 (II), No. 11 (1981), pp. 1932-1943 and English translation.

Von F. Lagler, F. Helm, V. Etzel und H. Kiel, *Toxikologische Untersuchungen mit Tramadol, einem neuen Analgetikum*, Arzneimittel-Forschung, Drug Res. 28(I), Heft 1a (1978), pp. 164-172 and English translation.

Von G. Osterloh, E. Friderichs*, F. Felgenheuer*, W.A. Gunzler, Z. Henmi**, T. Kitano**, M. Nakamura**, H. Hayashi** und I. Ishii**, *Allgemeine pharmakologische Untersuchungen mit Tramadol, einem stark wirkenden Analgetikum*, Arzneimittel-Forschung, Drug Res. 28(I), Heft 1a (1978), pp. 135-151 and English translation.

Von E. Friderichs, F. Felgenhauer, P. Jongschaap und G. Osterloh, *Pharmakologische Untersuchungen zur Analgesie, Abhängigkeits- und Toleranzentwicklung von Tramadol, einem stark wirkenden Analgetikum*, Arzneimittel-Forschung Drug Res. 28(I), Heft 1a, pp. 122-134 and English translation.

L. Collart, C. Luthy, C. Favario-Constantin, P. Dayer, *Dualite de l'effet analgesique du tramadol chez l'homme*, Schwiz Med. Wochenschr. 1993:123:, pp, 2241-2243 and English translation.

E. Beubler, *Medikamentose Schmerztherapie: Kriterien, Möglichkeiten, Risken*, Therapiewoche Österreich 7,2 (1992), pp. 90-96 and English translation.

Kaiko, et al., *A Single-dose Study of the Effect of Food Ingestion and Timing of Dose Administration on the Pharmacokinetic Profile of 30mg Sustained-release Morphine Sulfate Tablets*, Current Therapeutic Research, pp. 869-878, vol. 47, No. 5, May 1990.

Kaiko, et al., *Controlled-release Morphine Bioavailability (MS Contin™ Tablets) in the Presence and Absence of Food.* The Hospice Journal, pp. 17-30, vol. 6(4) 1990.

Gourlay, et al., *the Reproducibility of Bioavailability of Oral Morphine from Solution under Fed and Fasted Conditions*, Journal of Pain and Symptom Management, vol. 6, No. 7, Oct. 1991, pp. 431-436.

Gourlay, et al., *Influence of a High-fat Meal on the Absorption of Morphine from Oral Solutions*, Clin. Pharmacol. Ther., Oct. 1989, pp. 403-468.

Physicians Desk Reference 1994, 48th Edition, pp. 1821-1824.

Advertisement: Roxanol SR., 1988 Roxane Labs, Inc.

R. Kaiko and T. Hunt, *Comparison of the Pharmacokinetic Profiles of Two Oral Controlled-Release Morphine Formulations in Healthy Young Adults*, Clin. Thera. vol. 13, No. 4, 1991, pp. 484-488.

Thomsen, L. Juul, *Prolonged Release Matrix Pellets Prepared by Melt Pelletization. Part IV: Drug Content, Drug Particle Size, and Binder Composition*, Pharmaceutical Technology Europa, (Oct. 1994), pp. 19-22.

McTaggart, C.M., et al., *The Evaluation of Formulation and Processing Conditions of a Melt Granulation Process*, Int. J. Pharm., vol. 19, No. 2, issued 1984, pp. 139-148.

El-Shanawany, S., *Sustained Release of Nitrofurantoin From Inert Wax Matrixes*, J. Controlled Release, vol. 26, No. 1, issued 1993, pp. 11-19.

S. Bloomfield, et al., *Analgesic Efficacy and Potency of Two Oral Controlled-Release Morphine Preparations*, Clin. Pharmacol. Ther., vol. 53, No. 4, 1993, pp. 469-478.

Advertisement, MS Contin™ 1986, 1987 The Purdue Frederick Company.

P. Flanders, et al., *The Control of Drug Releases From Conventional Melt Granulation Matrices*, Drug Development and Industrial Pharmacy, vol. 13, No. 6, (1987), pp. 1001-1022.

T. Schaefer, et al., *Melt granulation in a laboratory scale high shear mixer*, Drug Development and Industrial Pharmacy, vol. 16, No. 8, (1990), pp. 1249-1277.

Thompson, L. Juul et al., Schaefer, T., et al., *Prolonged Release Matrix Pellets Prepared by Melt Pelletization, I. Process Variables*, Drug Development and Industrial Pharmacy, vol. 19, No. 15, pp. 1867-1887.

Thomsen, L. Juul, et al., *Prolonged Release Matrix Pellets Prepared by Melt Pelletization, Part IV. Drug Content, Drug Particle Size, and Binder Composition*, Pharmaceutical Technology Europe, (Oct. 1994), pp. 19-24.

Thomsen, L. Juul, *Utilizing melt pelletization technique for the preparation of prolonged released products, Pelletization*, (material elaborated by Assistant Prof. Lars Juul Thomsen, Dept. of Pharmaceutics, Royal Danish School of Pharmacy for the DIE course "Pelletization Technology", Nov. 1992, Sectons I to VI.

SK Baveja et al., Int. J. Pharmaceutics, 41, (1988) p. 55-62.

Formulating for Controlled Release with METHOCEL® Premium Cellulose Ethers. The Dow Chemical Company, 1989.

M S Vasquez et al., Drug Dev. & Ind. Pharmacy, 18 (11&12), p. 1355-1378 (1992).

L W S Cheong et al., Pharm. Res 9 (11) p. 1510-1514 (1992).

Pharmazeutische Stoffliste 6th Ed., 1985 p. 196.

Rote Liste 1993 Nos. 05001 & 05008.

Derwent Abstract 92:64751.

Haltbarkeits-Herstellungdaten deutscher Arzneimittel p. 486.

Goodman and Gilmans, 8th Ed., 1990: p. 497.

Hunt, et al., Clin. Ther. vol. 13, No. 4, 1991, pp. 482-488.

Lee et al. Drugs 46(2), 1993, pp. 313-340.

The Merck Index 11th Ed., 1989.

Pharmazeutische Stoffliste 10. Auflage, p. 193, Nov. 1994.
Rote Liste 1992 Entry 05007.
PIL (Product Information Leaflet) about MST CONTINUS® tablets.
Graph of dissolution rates claimed in the patent EP 0 624 366.
The Physician's Desk Reference, 1994. Monograph on MS CONTIN® (MST CONTINUS®) tablets.
Copy from USPXXII with Supplements of Extended Release monographs.
METHOCEL, Colorcon Technical Information.
DA Alderman, Int. J. Pharm. Tech. and Prod. Mfr., 5(3) p. 1-9, 1984.
HE Huber et al., J. Pharm. Sci. 55 (9) Sep. 1966, p. 974-976.
Lin SY et al., Current Therapeutic Research 52(3), p. 486-492, Sep. 1992.
Handbook of Pharmaceutical Excipients, p. 138-140, 1986.
Aqualon Technical Information Bulletin VC-585, 1991.
P Colombo, Advanced Drug Delivery Reviews, 11 (1993) p. 37-57.
KV Ranga Rao et al., Int. J. Pharmaceutics, 48 (1988) p. 1-13.
JE Hogan, Drug Dev. & Ind. Pharmacy, 15 (6 & 7), p. 975-999 (1989).
JL Ford et al., Int. J. Pharmaceutics, 24 (1985) p. 327-338.
PB Daly et al. Int. J. Pharmaceutics, 18 (1984) p. 201-205.
H Lapidus et al., J. Pharm. Sci., 55(8), Aug. 1966, p. 840-843.
H Lapidus et al., J. Pharm. Sci., 57(8), Aug. 1968, p. 1292-1301.
Abstract of JP 54/092631, published Jul. 23, 1979.
Stanislaw Janicki and Zdzisiaw Jedras, *Slow-Release Microballs: Method of Preparation*, Acta. Pharm. Technol. 33(3) (1987), pp. 154-155.
B. Elsing and G. Blaschke, *Achiral and chiral high-performance liquid chromatographic determination of tramadol and its major metabolites in urine after oral administration of racemic tramadol*, Journal of Chromatography, 612 (1993), pp. 223-230.
C.H.W. Koks, A.P.E. Vielvoye-Kerkmeer, and J.H. Beijnen, *Tramadol (Tramal)*, Pharm. Weekbl. 1993: 128(4): 1298-1300.
W. Lintz and H. Uragg, *Quantitative Determination of Tramadol in Human Serum by Gas Chromatography—Mass Spectrometry*, Journal of Chromatography, 341 (1985), pp. 65-79.
Pharm. Res. 1992; Supp. 9:308, *Tramadol*, PPDM's 8207 and 8206.
J.M. Aiache and J. Hirtz, *Biopharmaceutics—Absolute Bioavailability of Tramal Suppositories*, Third European Congress of Biopharmaceutics and Pharmacokinetics Proceedings—vol. 1, p. 311.
W. Lintz, H. Barth, G. Osterloh, and E. Schmid-Bothelt, *Bioavailability of Enteral Formulations 1st Communication: Capsules*, Arzeimittal-Forschung, Drug Res. 36 (II) Nr. 8 (1986), pp. 1278-1283.
Clinical Pharm. & Ther. vol. 53, No. 2, *American Society for Clinical Pharmacology and Therapeutics*, P111-67, P111-68 and P111-69.
Jean-Marie Besson and Michael D. Vickers, *Tramadol Analgesia Synergy in Research and Therapy*, Drugs 47 (Suppl. 1):1-2, 1994, Adis International Limited.
Pierre Dayer, Laurence Collart and Jules Desmeules, *The Pharmacology of Tramadol*, Drugs 47 (Suppl. 1):3-7, 1994, Adis International Limited.
Abraham Sunshine, *New Clinical Experience with Tramadol*, Drugs 47(Supp. 1) 8-18, 1994, Adis International Limited.
Klaus A. Lehmann, *Tramadol for the Management of Acute Pain*, Drugs 47 (Supp. 1): 19-32, 1994, Adis International Limited.
Keith Budd, *Chronic Pain—Challenge and Response* , Drugs 47 (Suppl. 1):39-43, 1994, Adis International Limited.
Jordi Cami, Xavier Lamas and Magi Farre, *Acute Effects of Tramadol in Methadone-Maintained Volunteers*, Drugs 47 (Supp. 1):39-43, 1994, Adis International Limited.
C.H.W. Koks, A.P.E. Vielvoye-Kerkmeer, and J.H. Beijnen, *Tramadol (Tramal)*.
C. Rhoda Lee, Donna Mc Tavish and Eugene M. Surkin, "Tramadol, A Preliminary Review of its Pharmacodynamic Properties, and Therapeutic Potential in Acute and Chronic Pain States", Drugs 46(2):313-340, 1993, Adis International Limited.
Valerie Kayser, Jean-Marie Besson, and Gisele Gilbaud, *Evidence for a noradrenergic component in the antinociceptive effect of the analgesic agent tramadol in an animal model of clinical pain, the arthritic rat*, European Journal of Pharmacology, 224(1992), pp. 83-88.
Kenzie L. Preston, Donald R. Jasinksi and Margaret Testa, *Abuse potential and pharmacological comparison of tramadol and morphine*, Drug and Alcohol Dependence, 27 (1991), pp. 7-17.
Valerie Kayser, Jean-Marie Besson and Gisele Guilbaud, *Effects of the analgesic agent tramadol in normal and arthritic rats: comparison with the effects of different opioids, including tolerance and cross-tolerance to morphine*, European Journal of Pharmacology, 195 (1991) 37-45.
T. Murano, H. Yamamoto, N. Endo, Y. Kudo, N. Okada, Y. Masuda, and I. Yano,*Studies of Dependence on Tramadol in Rats*, Arzneimittel-Forschung, Drug Res. 28(I) Heft 1a (1978).
T. Yanagita, *Drug Dependence Potential of 1-(m-Methoxyphenil)-2-(dimethylaminomethyl)-cyclohesan-1-ol Hydrochloride (Tramadol) Tested in Monkeys*, Arzneimittel-Forschung Drug Res. 28(1), Heft 1a (1978), pp. 158-163.
Abraham Sunshine, MD, Nancy Z. Olson, MPS, Itic Zighelboim, MD. Ana DeCastro, RN, and Frederick L. Minn, MD, PhD, *Analgesic oral efficacy of tramadol hydrochloride in postoperative pain*, Clin. Pharmacol. Ter. (Jun. 1992), pp. 740-146.
Translation of Japanese Patent Publication No. 43 (1968) 20006, Detailed Description of the Invention.
M. Ahmend and R.P. Enever, *Formulation and Evaluation of Sustained Release Paracetamol Tablet*, Journal of Clinical and Hospital Pharmacy (1981) 6, pp. 27-38.
M.D. Vickers, D. O'Flaherty, S.M. Szekely, M. Read and J. Yoshizumi, *Tramadol: pain relief by an opioid without depression of respiration*, Anaesthesia, 1992, vol. 47, pp. 291-296.
G.M. Hanna, C.A. Lau-Cam and W.M. Plank, *Direct determination of the enantiomeric purity of tramadol hydrochloride by proton nuclear resonance (1H NMR spectroscopy with chiral lanthanide shift reagent.* Pharamzie 44 (1989), H. 5, pp. 321-325.
Martindale, The Extra Pharmacopoeia, 28th Ed., 198, 6263-c, Tramadol hydrochloride, pp. 1029-1030.
Anderson, H.O. & Christensen, H., *In vitro and in vivo investigations of a new timed-release dosage form of*

propoxyphene hydrochloride, Dansk tidsskrift for farmaci, vol. 43, 1969, pp. 117-126.
Schmidhammer, Helmut, *Synthesis and Biological Evaluation of 14-Alkoxymorphinans*, Helvetica Chimica Acta, vol. 72, 1989, pp. 1233-1239.
Schmidhammer, Helmut, *Synthesis, Structure Elucidation, and Pharmacological Evaluation of 5-Methyloxymorphone*, Helvetica Chimica Acta, vol. 71, 1988, pp. 1801-1804.
Schmidhammer, Helmut, *Synthesis and Biological Evaluation of 14-Alkoxymorphinans*, J. Med Chem, (1990) vol. 33, No. 4, pp. 1200-1206.
ROTE LISTE® Service GmbH, Rote Liste 1998, Section 05.
S.J. Carter and R. Woodford, "Long-Acting Oral Medicaments", Pharmacy Digest (1961) pp. 183-189.
Remington's Pharmaceutical Sciences, 1980, p. 1598.
Thomsen, L. Juul, et al., *Prolonged Release Matrix Pellets Prepared by Melt Pelletization II. Hydrophobic Substances as Meltable Binders*, Drug Development and Industrial Pharmacy, vol. 20, No. 7, (1984), pp. 1179-1197.

* cited by examiner

Fig. 1.

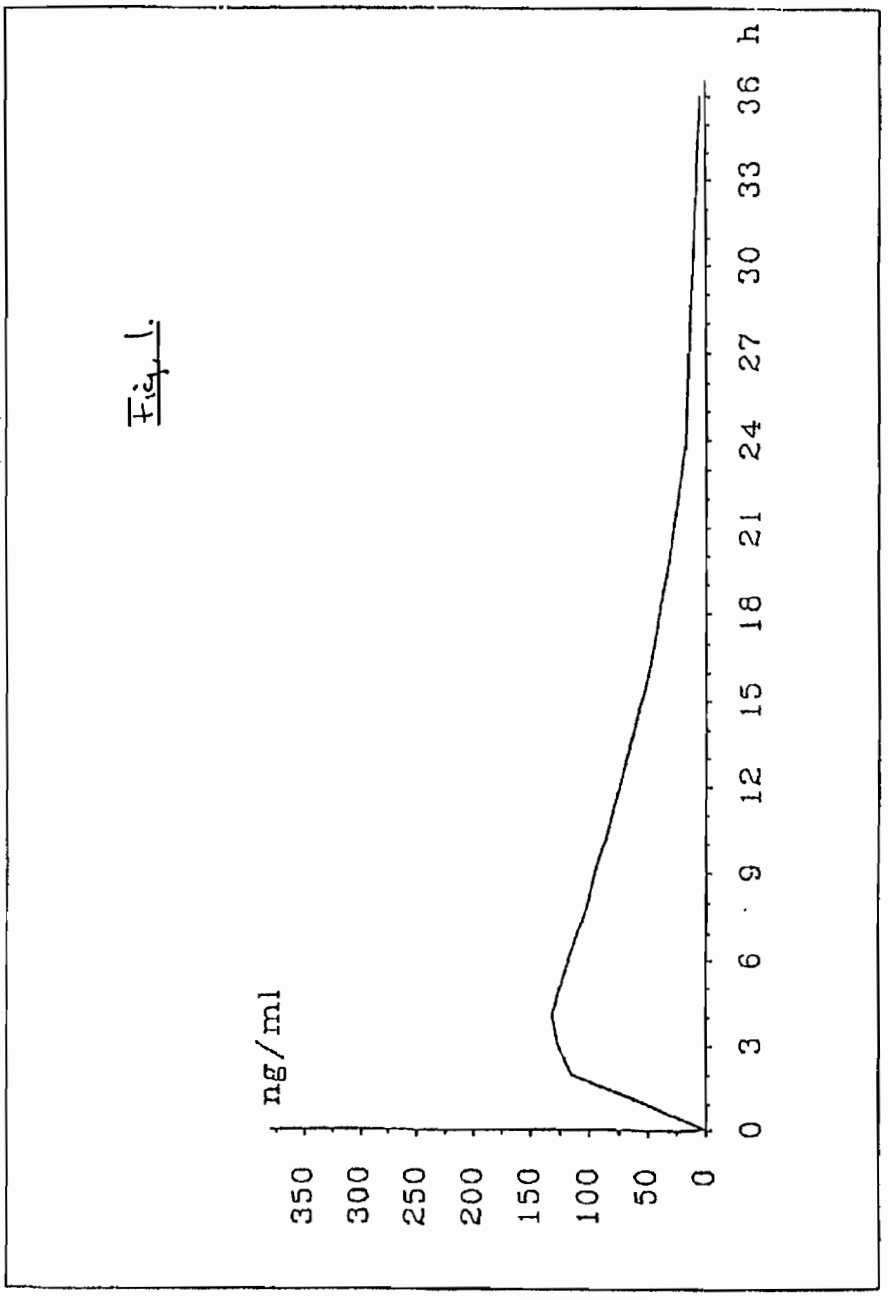
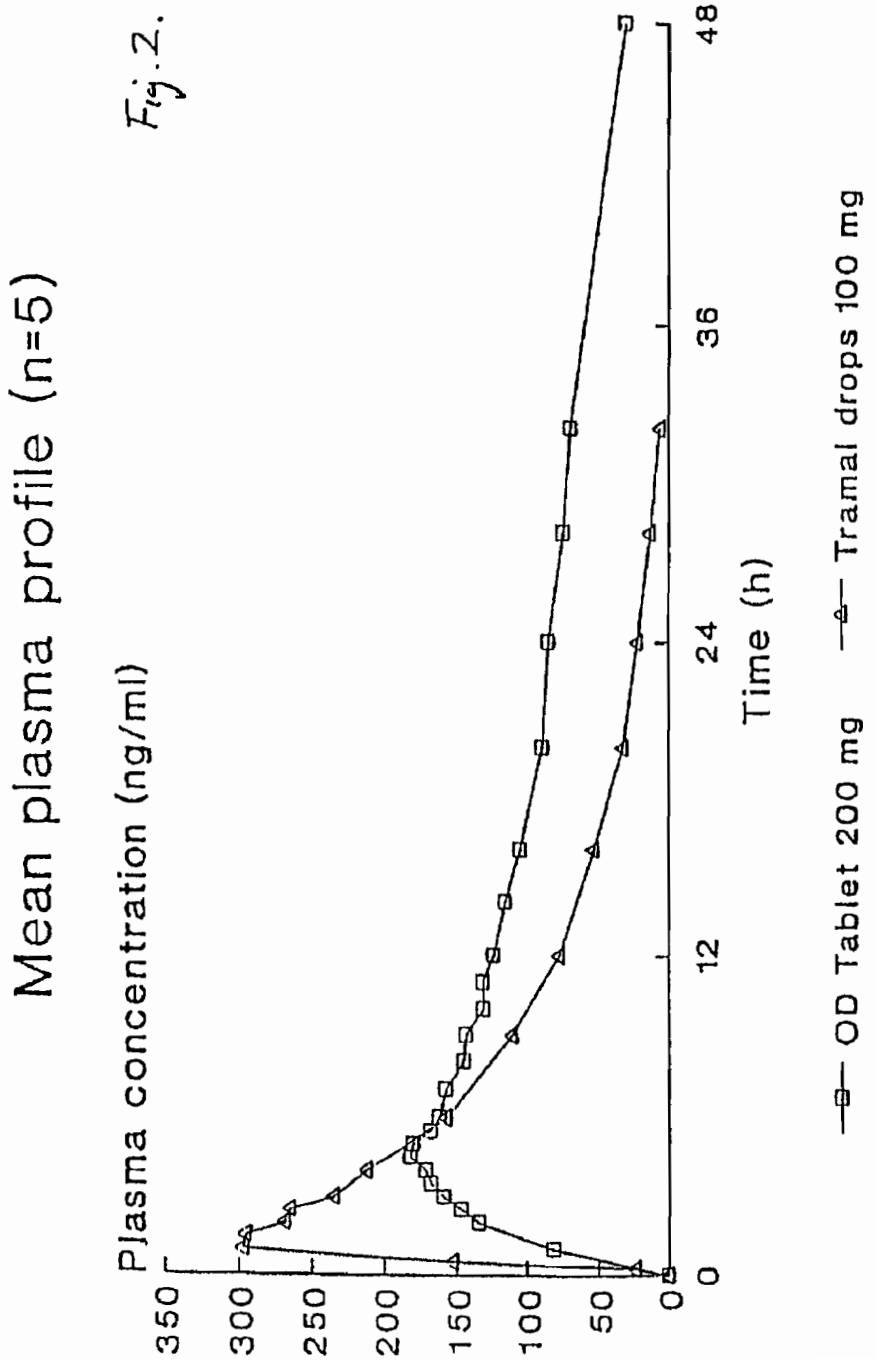


Fig. 2.


Mean plasma profile (n=5)
Plasma concentration (ng/ml)
350
300
250
200
150
100
50
0
0
12
24
36
48
Time (h)
OD Tablet 200 mg
Tramal drops 100 mg

CONTROLLED RELEASE TRAMADOL TRAMADOL FORMULATION

This application is a continuation of U.S. patent application Ser. No. 08/677,798, filed Jul. 10, 1996; now U.S. Pat. No. 6,254,887 which is a continuation of U.S. patent application Ser. No. 08/241,129, filed May 10, 1994 (now U.S. Pat. No. 5,591,452).

The present invention relates to a controlled release preparation for oral administration, to processes for its preparation and to its medical use. In particular, the invention relates to a controlled release preparation comprising tramadol or a pharmaceutically acceptable salt thereof.

Tramadol, which has the chemical name (±)-trans-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol, is an orally active opioid analgesic. Conventional release preparations in the form of capsules, drops and suppositories containing tramadol, or more particularly its hydrochloride salt, have been commercially available for many years for use in the treatment of moderate to severe pain; Such preparations, however, do not provide a controlled release of the tramadol. Moreover, despite tramadol's long-standing use, controlled release preparations for oral administration containing tramadol as active ingredient have not even previously been described in the literature.

It is an object of the present invention to provide an oral controlled release tramadol preparation suitable for at least twelve-hourly (e.g. up to twenty-four hourly) administration for the treatment of pain.

The present invention therefore provides a controlled release preparation comprising tramadol or a pharmaceutically acceptable salt thereof for oral administration.

Suitable pharmaceutically acceptable salts of tramadol for use according to the present invention are those conventionally known in the art such as pharmaceutically acceptable acid addition salts. The hydrochloride salt is particularly preferred.

A controlled release preparation according to the present invention is one that achieves slow release of a drug over an extended period of time, thereby extending the duration of drug action over that achieved by conventional delivery. Preferably such a preparation maintains a drug concentration in the blood within the therapeutic range for 12 hours or more.

The present inventors have found that in order to allow for controlled release tramadol over at least a twelve hour-period following oral administration, the in vitro release rate preferably corresponds to the following % rate of tramadol released:

TABLE 1

TIME (H)	% RELEASED
1	0–50
2	0–75
4	3–95
8	10–100
12	20–100
16	30–100
24	50–100
36	>80

Another preferred preparation especially suited for twice-a-day dosing has an in vitro release rate corresponding to the following % rate of tramadol released:

TABLE 2

TIME (H)	% RELEASED
1	20–50
2	40–75
4	60–95
8	80–100
12	90–100

Yet another preferred preparation particularly suited for once-a-day dosing has an in-vitro release rate corresponding to the following % rate of tramadol released:

TABLE 3

TIME (H)	% RELEASED
1	0–50
2	0–75
4	10–95
8	35–100
12	55–100
16	70–100
24	>90

A still further preferred preparation in accordance with the invention also particularly suited for once-a-day dosing has an in vitro release rate corresponding to the following % rate of tramadol released.

TABLE 4

TIME (H)	% RELEASED
1	0–30
2	0–40
4	3–55
8	10–65
12	20–75
16	30–88
24	50–100
36	>80

More preferably a preparation for once-a-day dosing has an in vitro release rate substantially as follows:

TIME (H)	% TRAMADOL RELEASED
1	15–25
2	25–35
4	30–45
8	40–60
12	55–70
16	60–75

Another preferred dissolution rate in vitro upon release of the controlled release preparation twice daily according to the invention, is between 5 and 50% (by weight) tramadol released after 1 hour, between 10 and 75% (by weight) tramadol released after 2 hours, between 20 and 95% (by weight) tramadol released after 4 hours, between 40 and 100% (by weight) tramadol released after 8 hours, more than 50% (by weight) tramadol released after 12 hours, more than 70% (by weight) released after 18 hours and more than 80% (by weight) tramadol released after 24 hours.

Furthermore, it is preferred in the case of a controlled release preparation for administration twice daily that after 8 hours following oral administration between 70 and 95% (by weight) tramadol is absorbed in vivo, between 77 and

97% (by weight) tramadol is absorbed after 10 hours and between 80 and 100% (by weight) tramadol is absorbed after 12 hours.

A formulation in accordance with the invention suitable for twice-a-day dosing may have a tmax of 1.5 to 8 hours, preferably 2 to 7 hours, and a W_{50} value in the range 7 to 16 hours.

A formulation in accordance with the invention suitable for once-a-day dosing may have a tmax in the range of 3 to 6 hours, preferably 4 to 5 hours and a W_{50} value in the range of 10 to 33 hours.

The W_{50} parameter defines the width of the plasma profile at 50% Cmax, i.e. the duration over which the plasma concentrations are equal to or greater than 50% of the peak concentration. The parameter is determined by linear interpolation of the observed data and represents the difference in time between the first (or only) upslope crossing and the last (or only) downslope crossing in the plasma profile.

The in vitro release rates mentioned herein are, except where otherwise specified, those obtained by measurement using the Ph. Eur. Paddle Method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37° C. and using UV detection at 270 nm.

The in viva absorption rate is determined from measurement of plasma concentration against time using the deconvolution techniqiue. A conventional release tramadol drop preparation (Tramal (trade mark), Grunenthal) was used as the weighting-function and the elimination half life of tramadol was taken as 7.8 hours.

The controlled release preparation according to the invention preferably contains an analgesically effective amount of tramadol or a pharmaceutically acceptable salt thereof, conveniently in the range of from 50 to 800 mg, especially 100, 200, 300, 400 to 600 mg (calculated as tramadol hydrochloride) per dosage unit.

The controlled release preparation according to the invention may be presented, for example, as granules, spheroids, pellets, multiparticulates, capsules, tablets, sachets, controlled release suspensions, or in any other suitable dosage form incorporating such granules, spheroids, pellets or multiparticulates.

The active ingredient in the preparation according to the invention may suitably be incorporated in a matrix. This may be any matrix that affords controlled release tramadol over at least a twelve hour period and preferably that affords in-vitro dissolution rates and in vivo absorption rates of tramadol within the ranges specified above. Preferably the matrix is a controlled release matrix. Alternatively, normal release matrices having a coating which provides for controlled release of the active ingredient may be used.

Suitable materials for inclusion in a controlled release matrix include

(a) Hydrophillic or hydrophobic polymers, such as gums, cellulose ethers, acrylic resins and protein derived materials. Of these polymers, the cellulose ethers, especially alkylcelluloses are preferred. The preparation may conveniently contain between 1% and 80% (by weight) of one or more hydrophillic or hydrophobic polymers.

(b) Digestible, long chain (C_8–C_{50}, especially C_{12}–C_{40}), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils and waxes. Hydrocarbons having a melting point of between 25 and 90° C. are preferred. Of these long chain hydrocarbon materials, fatty (aliphatic) alcohols are preferred. The preparation may conveniently contain up to 60% (by weight) of at least one digestible, long chain hydrocarbon.

(c) Polyalkylene glycols. The preparation may suitably contain up to 60% (by weight) of one or more polyalkylene glycols.

One particularly suitable controlled release matrix comprises one or more alkylcelluloses and one or more C_{12}–C_{36} aliphatic alcohols. The alkylcellulose is preferably C_1–C_6 alkyl cellulose, especially ethyl cellulose. The controlled release preparation according to the invention preferably contains from 1 to 20% (by weight), especially from 2 to 15% (by weight) of one or more alkylcelluloses.

The aliphatic alcohol may conveniently be lauryl alcohol, myristyl alcohol or stearyl alcohol but is preferably cetyl alcohol or more preferably cetostearyl alcohol. The controlled release preparation suitably contains from 5 to 30% (by weight) of aliphatic alcohol, especially from 10 to 25% (by weight) of aliphatic alcohol.

Optionally the controlled release matrix may also contain other pharmaceutically acceptable ingredients which are conventional in the pharmaceutical art such as diluents, lubricants, binders, granulating aids, colourants, flavourants, surfactants, pH adjusters, anti-adherents and glidants, e.g. dibutyl sebacate, ammonium hydroxide, oleic acid and colloidal silica.

The controlled release preparation according to the invention may conveniently be film coated using any film coating material conventional in the pharmaceutical art. Preferably an aqueous film coating is used.

Alternatively, the controlled release preparation according to the invention may comprise a normal release matrix having a controlled release coating. Preferably the preparation comprises film coated spheroids containing the active ingredient and a spheronising agent.

The spheronising agent may be any suitable pharmaceutically acceptable material which may be spheronised together with the active ingredient to form spheroids. A preferred spheronising agent is microcrystalline cellulose. The microcrystalline cellulose used may suitably be, for example, Avicel PH 101 or Avicel PH 102 (Trade Marks, FMC Corporation).

Optionally the spheroids may contain other pharmaceutically acceptable ingredients conventional in the pharmaceutical art such as binders, bulking agents and colourants. Suitable binders include water soluble polymers, water soluble hydroxyalkyl celluloses such as hydroxypropylcellulose or water insoluble polymers (which may also contribute controlled release properties) such as acrylic polymers or copolymers for example ethylcellulose. Suitable bulking agents include lactose.

The spheroids are coated with a material which permits release of the active ingredient at a controlled rate in an aqueous medium. Suitable controlled release coating materials include water insoluble waxes and polymers such as polymethacrylates (for example Eudragit polymers, Trade Mark) or water insoluble celluloses, particularly ethylcellulose. Optionally, water soluble polymers such as polyvinylpyrrolidone or water soluble celluloses such as hydroxypropylmethylcellulose or hydroxypropylcellulose may be included. Optionally other water soluble agents such as polysorbate 80 may be added.

Alternatively the drug may be coated onto inert non-pareil beads and the drug loaded beads coated with a material which permits control of the release of the active ingredient into the aqueous medium.

In a further aspect the present invention provides a process for preparing a controlled release preparation

according to the present invention comprising incorporating tramadol or a pharmaceutically acceptable salt thereof in a controlled release matrix, for example by

(a) granulating a mixture comprising tramadol or a pharmaceutically acceptable salt thereof and one or more alkylcelluloses,

(b) mixing the alkylcellulose containing granules with one or more C_{12-36} aliphatic alcohols; and optionally

(c) shaping and compressing the granules, and film coating, if desired; or

(d) granulating a mixture comprising tramadol or a pharmaceutically acceptable salt thereof, lactose and one or more alkylcelluloses with one or more C_{12-36} aliphatic alcohol; and, optionally,

(e) shaping and compressing the granules, and film coating, if desired.

The controlled release preparation according to the invention may also be prepared in the form of film coated spheroids by

(a) granulating the mixture comprising tramadol or a pharmaceutically acceptable salt thereof and a spheronising agent;

(b) extruding the granulated mixture to give an extrudate;

(c) spheronising the extrudate until spheroids are formed; and

(d) coating the spheroids with a film coat.

One preferred form of unit dose form in accordance with the invention comprises a capsule filled with controlled release particles essentially comprising the active ingredient, a hydrophobic fusible carrier or diluent and optionally a hydrophillic release modifier. In particular, the controlled release particles are preferably prepared by a process which comprises forming a mixture of dry active ingredient and fusible release control materials followed by mechanically working the mixture in a high speed mixer with an energy input sufficient to melt or soften the fusible material whereby it forms particles with the active ingredient. The resultant particles, after cooling, are suitably sieved to give particles having a size range from 0.1 to 3.0 mm, preferably 0.25 to 2.0 mm. An example according to the invention is described below which is suitable for the commercial production of dosage units.

When using such a processing technique it has been found that, in order most readily to achieve the desired release characteristics (both in vivo and in vitro as discussed above) the composition to be processed should comprises two essential ingredients namely:

(a) tramadol or salt thereof; and

(b) hydrophobic fusible carrier or diluent; optionally together with

(c) a release control component comprising a water-soluble fusible material or a particulate soluble or insoluble organic or inorganic material.

We have found that the total amount of tramadol or pharmaceutically acceptable salt thereof in the composition may vary within wide limits, for example from 10 to 90% by weight thereof.

The hydrophobic fusible component (b) should be a hydrophobic material such as a natural or synthetic wax or oil, for example hydrogenated vegetable oil, hydrogenated castor oil, microcrystalline wax, Beeswax, Carnauba wax or glyceryl monostearate, and suitably has a melting point of from 35 to 140° C., preferably 45 to 110° C.

The release modifying component (c), when a water soluble fusible material, is conveniently a polyethylene glycol and, when a particulate material, is conveniently a pharmaceutically acceptable material such as dicalcium phosphate or lactose.

Another preferred process for the manufacture of a formulation in accordance with the invention comprises

(a) mechanically working in a high-speed mixer, a mixture of tramadol or a pharmaceutically acceptable salt in particulate form and a particulate, hydrophobic fusible carrier or diluent having a melting point from 35 to 140° C. and optionally a release control component comprising a water soluble fusible material, or a particulate soluble or insoluble organic or inorganic material at a speed and energy input which allows the carrier or diluent to melt or soften, whereby it forms agglomerates,

(b) breaking down the larger agglomerates to give controlled release seeds; and

(c) continuing mechanically working with optionally a further addition of low percentage of the carrier or diluent.

(d) optionally repeating steps (c) and possibly (b) one or more times.

This process is capable of giving a high yield (over 80%) of particles in a desired size range, with a desired uniformity of release rate of tramadol or salt thereof.

The resulting particles may be sieved to eliminate any over-or undersized material then formed into the desired dosage units by for example, encapsulation into hard gelatin capsules containing the required dose of the active substance or by compression into tablets.

In this method in accordance with the invention preferaby all the tramadol or salt thereof is added in step (a) together with a major portion of the hydrophobic fusible release control material used. Preferably the amount of fusible release control material added in step (a) is between 10% and 90% w/w of the total amount of ingredients added in the entire manufacturing operation, more preferably between 20% and 70% w/w.

Stage (a) of the process may be carried out in conventional high speed mixers with a standard stainless steel interior, e.g. a Collette Vactron 75 or equivalent mixer. The mixture is processed until a bed temperature about 40° C. or above is achieved and the resulting mixture acquires a cohesive granular texture, with particle sizes ranging from about 1–3 mm to fine powder in the case of non-aggregated original material. Such material, in the case of the embodiments described below, has the appearance of agglomerates which upon cooling below 40° C. have structural integrity and resistance to crushing between the fingers. At this stage the agglomerates are of an irregular size, shape and appearance.

The agglomerates are preferably allowed to cool. The temperature to which it cools is not critical and a temperature in the range room temperature to 37° C. may be conveniently used.

The agglomerates are broken down by any suitable means, which will comminute oversize agglomerates and produce a mixture of powder and small particles preferably with a diameter under 2 mm. It is currently preferred to carry out the classification using a Jackson Crockatt granulator using a suitable sized mesh, or a Comil with an appropriate sized screen. We have found that if too small a mesh size is used in the aforementioned apparatus the agglomerates melting under the action of the beater or impeller will clog the mesh and prevent further throughput of mixture, thus reducing yield. A mesh size of 12 has been found adequate.

The classified material is returned to the high speed mixer and processing continued. It is believed that this leads to cementation of the finer particles into particles of uniform size range.

In one preferred form of the method of the invention processing of the classified materials is continued, until the hydrophobic fusible materials used begin to soften/melt and optionally additional hydrophobic fusible material is then added. Mixing is continued until the mixture has been transformed into particles of the desired predetermined size range.

In order to ensure uniform energy input into the ingredients in the high speed mixer it is preferred to supply at least part of the energy by means of microwave energy.

Energy may also be delivered through other means such as by a heating jacket or via the mixer impeller and chopper blades.

After the particles have been formed they are cooled or allowed to cool, and may then be sieved to remove any over or undersized material.

The resulting particles may be used to prepare dosage units in accordance with the invention in the form of e.g. tablets or capsules in manners known per se.

We have also found that particles containing tramadol or a salt thereof produced by a melt processing as described in application PCT/SE93/00225 and the process described and claimed in our prior unpublished UK application No. 9324045.5 filed on 23 Nov. 1993 as well as the process described herein are particularly useful for processing into the form of tablets.

We have found that by suitable selection of the materials used in forming the particles and in the tabletting and the proportions in which they are used, enables a significant degree of control in the ultimate dissolution and release rates of the tramadol or salt thereof from the compressed tablets.

Usually, to form a tablet in accordance with the invention, particles prepared as described above will be admixed with tabletting excipients e.g. one or more of the standard excipients such as diluents, lubricants, binding agents, flow aids, disintegrating agents, surface active agents or water soluble polymeric materials.

Suitable diluents are e.g. microcrystalline cellulose, lactose and dicalcium phosphate. Suitable lubricants are e.g. magnesium stearate and sodium stearyl fumarate. Suitable binding agents are e.g. hydroxypropyl methyl cellulose, polyvidone and methyl cellulose.

Suitable disintegrating agents are starch, sodium starch glycolate, crospovidone and croscarmalose sodium.

Suitable surface active are Poloxamer 188®, polysorbate 80 and sodium lauryl sulfate.

Suitable flow aids are talc colloidal anhydrous silica.

Suitable water soluble polymers are PEG with molecular weights in the range 1000 to 6000.

To produce tablets in accordance with the invention, particles produced in accordance with the invention may be mixed or blended with the desired excipient(s), if any, using conventional procedures, e.g. using a Y-Cone or bin-blender and the resulting mixture compressed according to conventional tabletting procedure using a suitable size tabletting mould. Tablets can be produced using conventional tabletting machines, and in the embodiments described below were produced on standard single punch F3 Manesty machine or Kilian RLE15 rotary tablet machine.

Generally speaking we find that even with such a highly water soluble active agent as tramadol or salt thereof tablets formed by compression according to standard methods give very low release rates of the active ingredient e.g. corresponding to release over a period of greater than 24 hours, say more than 36. We have found that the release profile can be adjusted in a number of ways. For instance a higher loading of the drug will be associated with increased release rates; the use of larger proportions of the water soluble fusible material in the particles or surface active agent in the tabletting formulation will also be associated with a higher release rate of the active ingredient. By controlling the relative amounts of these ingredients it is possible to adjust the release profile of the tramadol or salt thereof.

In order that the invention may be well understood the following examples are given by way of illustration only.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention is further illustrated with the accompanying drawings in which:

FIG. 1 is a graphical depiction of the serum levels of tramadol following administration of one tablet according to Example 2 in 12 healthy volunteers; and

FIG. 2 is a graphical depiction of the plasma profile resulting from single dose administration of the tablet of Example 8 in comparison to the administration of a commercial preparation of tramadol drops 100 mg in a trial involving five healthy male volunteers.

EXAMPLE 1

Tablets having the following formulation were prepared:

	mg/tablet
Tramadol Hydrochloride	100
Lactose Ph. Eur.	68.0
Ethylcellulose (Surelease ® 25% solids)	15
Purified Water Ph. Eur.	13.3*
Cetostearyl Alcohol Ph. Eur. (Dehydag wax O)	42.00
Magnesium Stearate Ph. Eur.	2.00
Purified Talc Ph. Eur.	3.00
	230.00

*Removed during processing.

Tramadol hydrochloride (100 mg) and lactose (68 mg) were granulated, transferred to a fluid bed granulator and sprayed with ethylcellulose (15 mg) and water. The granules were then dried at 60° C. and passed through a 1 mm screen.

To the warmed tramadol containing granules was added molten cetostearyl alcohol (42 mg) and the whole was mixed thoroughly. The granules were allowed to cool and sieved through a 1.6 mm screen. Purified talc and magnesium stearate were added and mixed with the granules. The granules were then compressed into tablets.

The tablets were coated with a film coat having the formulation given below.

	mg/tablet
Hydropropylmethylcellulose Ph. Eur. 15 cps (Methocel E15)	0.770
Hydroxypropylmethylcellulose (Ph. Eur. 5 cps (Methocel E5)	3.87
Opaspray M-1-7111B (33% solids)	2.57
Polyethylene glycol 400 USNF	0.520

-continued

	mg/tablet
Purified Talc Ph. Eur.	0.270
Purified Water Ph. Eur.	55.52*

*Remove during processing.

EXAMPLE 2

Tablets having the following formulation were prepared:

	mg/tablet
Tramadol hydrochloride	100.0
Lactose Ph. Eur.	58.0
Ethylcellulose USNF (Ethocel 45 CP)	15.0
Cetostearyl alcohol Ph. Eur. (Dehydag wax O)	52.0
Magnesium stearate Ph. Eur.	2.00
Purified talc Ph. Eur.	3.00

A mixture of tramadol hydrochloride (100 mg), lactose (58 mg) and ethylcellulose (15 mg) was granulated whilst adding molten cetostearyl alcohol (52 mg) and the whole was mixed thoroughly. The granules were allowed to cool and sieved through a 1.6 mm screen. Purified talc and magnesium stearate were added and mixed with the granules. The granules were then compressed into tablets which were coated with a film coat having the formulation given in Example 1.

EXAMPLE 3

Film coated tablets were produced following the procedure described in Example 2 and having the following formulation:

	mg/tablet
Tramadol hydrochloride	100.00
Lactose Ph. Eur.	70.50
Hydroxyethylcellulose Ph. Eur.	12.50
Cetostearyl alcohol Ph. Eur.	42.00
Magnesium stearate Ph. Eur.	2.00
Purified talc Ph. Eur.	3.00

In Vitro Dissolution Studies

In vitro dissolution studies were conducted on tablets prepared as described above. Results are given in Table 1.

TABLE 1

	WT % TRAMADOL RELEASED		
Time (h)	Example 1	Example 2*	Example 3
1	39	35	43
2	52	47	60
4	67	62	84
8	82	78	97
12	90	86	—

*Measured on tablet core

In a trial involving 12 healthy volunteers the serum levels of tramadol following administration of one tablet according to Example 2 was found to be as illustrated in FIG. 1.

EXAMPLES 4 AND 5

Particles having the formulations given in Table II below were prepared by the steps of:

i. Placing the ingredients (a) and (c) (total batch weight 0.7 kg) in the bowl of a liter capacity Collette Gral Mixer (or equivalent) equipped with variable speed mixing and granulating blades;

ii. Mixing the ingredients at about 150–1000 rpm whilst applying heat until the contents of the bowl are agglomerated.

iii. Classifying the agglomerated material by passage through a Comil and/or Jackson Crockatt to obtain controlled release seeds.

iv. Warming and mixing the classified material in the bowl of a 10 liter Collette Gral, until uniform multiparticulates of the desired pre-determined size range are formed in yield of greater than 80%. This takes approximately 5 minutes.

v. Discharging the multiparticulates from the mixer and sieving them to separate out the multiparticulates collected between 0.5 and 2 mm aperture sieves.

TABLE II

Example	4	5
(a) Tramadol HCl (Wt %)	50	75
(b) Hydrogenated Vegetable Oil (Wt %)	50	25

EXAMPLE 6

Samples of the particles from Example 4 were blended with magnesium stearate and purified talc using a Y-Cone or bin-blender. The blended mixture was then compressed using either (1) 14x6 mm, (2) 16x7 mm or (3) 18.6x7.5 mm capsule shaped tooling on a single punch F3 Manesty tabletting machine to give tablets giving 200, 300 and 400 mg of tramadol HCl. The ingredients per dosage unit amounted to the following:

TABLE III

TABLET	MG/TABLET		
INGREDIENT	1	2	3
Tramadol HCl	200	300	400
Hydrogenated Vegetable Oil	200	300	400
Sub Total	400	600	800
Purified Talc	12.63	18.95	25.26
Magnesium Searate	8.42	12.63	16.84

The tablets were assessed by the dissolution using Ph. Eur. Paddle Method 100 rpm, 0.1 N HCl.

To assess the non-compressed particles the Ph Eur. Paddle was replaced by a modified Ph Eur. Basket.

The results are shown in Table IV below;

TABLE IV

HOURS AFTER START OF TEST	Particles	Tablet 1	Tablet 2	Tablet 3
	% TRAMADOL HCl RELEASED			
1	54	16	15	15
2	68	23	20	21
3	76	28	25	25
4	82	32	28	28
6	89	40	35	35
8	93	46	41	40
10	96	50	45	45
12	98	55	49	49
16	100	63	57	56
20	NR	70	63	NR

These results confirm the effectiveness of the tabletting in reducing the release rate.

EXAMPLE 7

Samples of the particles from Example 5 were then tabletted using a procedure similar to Example 3 and the ingredients per unit dosage amounted to:

TABLE V

TABLET	MG/TABLET		
INGREDIENT	4	5	6
Tramadol HCl	200	300	400
Hydrogeziated Vegetable Oil	66.7	100	133
Sub Total	266.7	400	533
Purified Talc	7.63	11.44	15.25
Magnesium Stearate	5.16	7.63	10.17

The tablets and samples of non-compressed multiparticulates (each sample containing 400 mg of tramadol hydrochloride) were assessed by the dissolution method also described above. The results are shown in Table VI below;

TABLE VI

HOURS AFTER START OF TEST	Particles	Tablet 4	Tablet 5	Tablet 6
	% TRAMADOL HCl RELEASED			
1	77	43	40	42
2	92	64	55	56
3	98	75	65	66
4	100	83	72	73
6	102	94	83	84
8	102	100	91	91
10	102	NR	96	97

These results show that by increasing the loading of the highly water soluble tramadol hydrochloride (75% w/w in this example compared with 50% w/w in Example 6) a significantly faster release rate of the active ingredient can be achieved.

EXAMPLE 8

Example 4 was repeated but with the following formulation:

Tramadol HCl	200 mg/tablet
Hydrogenated Vegetable Oil	163.0 mg/tablet

The resulting multiparticulates were blended as described in Example 6 with the following;

Purified Talc	11.5 mg/tablet
Magnesium Stearate	7.66 mg/tablet

The blend was then compressed as described in Example 6 but using 15 mm×6.5 mm normal concave capsule shaped plain/plain punches.

The resulting tablets were then assessed by the dissolution method described above. The results are shown in Table V.

HOURS AFTER START OF TEST	% TRAMADOL HCl RELEASED
1	20
2	27
3	32
4	37
6	44
8	50
10	55
12	60
16	67
20	73
24	77

In a trial involving five healthy male volunteers the plasma profile resulting from single dose administrations of the above tablet are shown in FIG. 2 in comparison to the administration of a commercial preparation of Tramadol drops 100 mg.

What is claimed is:

1. A solid controlled release oral dosage form, comprising,

a therapeutically effective amount of tramadol or a pharmaceutically acceptable salt thereof incorporated into a normal release matrix,

said matrix overcoated with a controlled release coating comprising a polymethacrylate or a water insoluble cellulose,

said dosage form providing a therapeutic effect for at least about 24 hours.

2. The controlled release dosage form as claimed in claim 1, wherein said controlled release coating comprises a polymethacrylate.

3. The controlled release dosage form as claimed in claim 1, wherein said controlled release coating comprises a water insoluble cellulose.

4. The controlled release dosage form as claimed in claim 2, wherein said controlled release coating further comprises a water soluble cellulose.

5. The controlled release dosage form as claimed in claim 3, wherein said controlled release coating further comprises a polyvinylpyrrolidone.

6. The controlled release dosage form as claimed in claim 1, containing from about 50 to 800 mg of tramadol or a pharmaceutically acceptable salt thereof, calculated as the hydrochloride salt.

7. The controlled release dosage form as claimed in claim 1, having a dissolution rate in-vitro when measured using the Ph. Eur. Paddle Method at 100 rpm in 900 ml 0.1N hydrochloric acid at 37° C. and using UV detection at 270 nm, from about 0 to about 50% tramadol released after 1 hour; from about 0 to about 75% tramadol released after 2 hours; from about 10 to about 95% tramadol released after 4 hours; from about 35 to about 100% after 8 hours; from about 55 to about 100% tramadol released after 12 hours; from about 70 to about 100% tramadol released after 16 hours; and greater than 90% tramadol released after 24 hours, by weight.

8. The controlled release dosage form as claimed in claim 1, having a dissolution rate in-vitro when measured using the Ph. Eur. Paddle Method at 100 rpm in 900 ml 0.1N hydrochloric acid at 37° C. and using UV detection at 270 nm, from about 0 to about 30% tramadol released after 1 hour; from about 0 to about 40% tramadol released after 2 hours; from about 3 to about 55% tramadol released after 4 hours; from about 10 to about 65% after 8 hours; from about 20 to about 75% tramadol released after 12 hours; from about 30 to about 88% tramadol released after 16 hours; from about 50 to about 100% tramadol released after 24 hours and greater than 80% tramadol released after 36 hours, by weight.

9. The controlled release dosage form as claimed in claim 1, having a dissolution rate in-vitro when measured using the Ph. Eur. Paddle Method at 100 rpm in 900 ml 0.1N hydrochloric acid at 37° C. and using UV detection at 270 nm, from about 15 to about 25% tramadol released after 1 hour; from about 25 to about 35% tramadol released after 2 hours; from about 30 to about 45% tramadol released after 4 hours; from about 40 to about 60% after 8 hours; from about 55 to about 70% tramadol released after 12 hours; and from about 60 to about 75% tramadol released after 16 hours, by weight.

10. The dosage form according to claim 1, which provides a t_{max} from about 3 to about 6 hours.

11. The dosage form according to claim 1, which provides a W_{50} from about 10 to about 33 hours.

12. The dosage form according to claim 3 wherein said water insoluble cellulose comprises ethylcellulose.

13. The dosage form of claim 1, comprising 100 mg tramadol hydrochloride.

14. The dosage form of claim 1, comprising 200 mg tramadol hydrochloride.

15. The dosage form of claim 1, comprising 300 mg tramadol hydrochloride.

16. The dosage form of claim 1, comprising 400 mg tramadol hydrochloride.

17. The dosage form of claim 1, comprising 600 mg tramadol hydrochloride.

* * * * *

EXHIBIT 3

27th Edition

DORLAND'S ILLUSTRATED

Medical Dictionary

W.B. SAUNDERS COMPANY
Harcourt Brace Jovanovich, Inc.
Philadelphia London Toronto
Montreal Sydney Tokyo

Dorland's illustrated medical dictionary.
Philadelphia: W.B. Saunders Co.,

v.: ill.; 27 cm.

Irregular.
Began publication with 23rd ed.
Description based on: 26th ed.
Continues: American illustrated medical dictionary.

1. Medicine—Dictionaries. I. Dorland, W.A. Newman (William Alexander Newman), 1864–1956.
[DNLM: 1. Dictionaries, Medical. 2. Reference Books, Medical]

R121.D73 610'.3'21—dc19 0-6383
AACR 2 MARC-S

Library of Congress [8607r85]rev6

W.B. SAUNDERS COMPANY
Harcourt Brace Jovanovich, Inc.
The Curtis Center
Independence Square West
Philadelphia, PA 19106

Listed here are the latest translated editions of this book together with the languages for the translations and the publishers.

Italian *(26th Edition, revised)*—Edizioni Scientifiche Internazionali (ESI), Milan, Italy

Japanese *(26th Edition)*—Hirokawa Publishing Company, Tokyo, Japan

Spanish *(26th Edition)* (Adaption)—Nueva Editorial Interamericana, Mexico City, Mexico

Managing Editor, Dictionaries: Elizabeth J. Taylor
Editors: Douglas M. Anderson, Joseph M. Patwell, Katharine Plaut, Kathleen McCullough
Production Manager: Carolyn Naylor
Illustrator: Sharon Iwanczuk
Illustration Coordinator: Walt Verbitski
Mechanical Artist: Melissa Walter

Dorland's Illustrated Medical Dictionary ISBN 0-7216-3154-1

Library of Congress catalog card number 78–50050

Last digit is the print number: 9 8 7 6 5 4

the lungs through phylogeny. **target t.,** the theory advanced to explain some biological effects of radiation on the basis of ionization occurring in a very small sensitive region within the cell, which postulates that one or more ionizing events, or "hits," within the sensitive volume are necessary to bring about the biological end-effect; called also *hit t.* **template t.,** a theory of the mechanism of antibody specificity, current during the 1930s and 40s, which proposed that the shape of an antibody molecule is determined as it is synthesized by being molded on an antigen molecule. The antigen thus "instructs" a cell to make specific antibody. Called also *instructive t.* **thermostat t.,** a theory which suggests that the feeding and satiety centers of the brain, like the thermoregulatory centers, are sensitive to body temperature; a decrease in body temperature activates the feeding center and depresses the satiety center, whereas increased temperature acts on the centers in the opposite way. **Traube's resonance t.,** resonance t., def. 2. **trialistic t.,** the theory that the blood cells arise from three distinct types of primitive cells, the myeloblasts, lymphoblasts, and monocytes. Cf. *dualistic t.*, *monophyletic t.*, and *polyphyletic t.* **undulatory t.,** wave t. **unitarian t.,** monophyletic t. **unitary t.,** the theory that disease is single in its nature and is not made up of separate and distinct morbid entities. **wave t.,** the theory that light, heat, and electricity are transmitted through space in the form of waves. **Weismann's t.,** see *weismannism*. **Woods-Fildes t.,** the theory that the antibacterial activity of at least some chemotherapeutic drugs (especially the sulfonamides) is a consequence of a competitive inhibition of essential metabolic reactions of the microorganism. **Young-Helmholtz t.,** the doctrine that color vision depends on three sets of retinal fibers, corresponding to the colors red, green, and violet. **Zuntz's t.,** a theory of muscle contraction.

theotherapy (the″o-ther′ah-pe) [Gr. *theos* god + *therapy*] the treatment of disease by prayer and religious exercises.

Thephorin (thef′o-rin) trademark for preparations of phenindamine tartrate.

theque (tēk) [Fr. a "box or small chest"] a round or oval collection, or nest, of melanin-containing nevus cells occurring at the dermoepidermal junction of the skin or in the dermis proper.

therapeusis (ther″ah-pu′sis) therapeutics.

therapeutic (ther″ah-pu′tik) [Gr. *therapeutikos* inclined to serve] 1. pertaining to therapeutics, or to the art of healing. 2. curative.

therapeutics (ther″ah-pu′tiks) 1. the science and art of healing. 2. a scientific account of the treatment of disease.

therapeutist (ther″ah-pu′tist) therapist.

Theraphosidae (ther″ah-fo′sĭ-de) a family of very large hairy spiders (suborder Orthognatha) found in temperate and tropical areas. *Sericopelma communis* is the only species whose venom has a harmful effect on man, but some are capable of inflicting painful bites. The members of this family are sometimes improperly called tarantulas.

therapia (ther″ah-pi′ah) [L., from Gr.] therapy. **t. sterilisans magna,** Ehrlich's procedure of treatment by the use of some chemical agent which will destroy the parasites in the body of a patient without being seriously toxic for the patient.

therapist (ther′ah-pist) [Gr. *therapeutēs* one who attends to the sick] a person skilled in the treatment of disease; often combined with a term indicating the specific type of disorder treated (as *speech therapist*) or a particular type of treatment rendered (as *physical therapist*). **physical t.,** a person skilled in the techniques of physical therapy and qualified to administer treatments prescribed by a physician and under his supervision; called also *physiotherapist*. **speech t.,** a person specially trained and qualified to assist patients in overcoming speech and language disorders.

therapy (ther′ah-pe) [Gr. *therapeia* service done to the sick] the treatment of disease; therapeutics. See also under *treatment*. **anticoagulant t.,** the use of drugs to render the blood sufficiently incoagulable to discourage thrombosis. **autoserum t.,** treatment of disease by the injection of the patient's own blood serum. **aversion t.,** therapy directed at associating an undesirable behavior pattern with unpleasant stimulation or at making the unpleasant stimulation a consequence of the undesirable behavior. **beam t.,** 1. treatment by exposure to light from one of the colors of the spectrum. 2. treatment by radiation emitted from a source located at a distance from the body. **behavior t.,** a therapeutic approach in which the focus is on the patient's observable behavior, rather than on conflicts and unconscious processes presumed to underlie his maladaptive behavior. This is accomplished through systematic manipulation of the environmental and behavioral variables related to the specific behavior to be modified; operant conditioning, systematic desensitization, token economy, aversive control, flooding, and implosion are examples of techniques that may be used in behavior therapy. Called also *behavior modification* and *conditioning therapy*. **biological t.,** treatment of disease by the injection of the substances which produce a biological reaction in the organism. The term includes the use of sera, antitoxins, vaccines, and nonspecific proteins. **buffer t.,** intravenous injection of buffer substances, such as sodium bicarbonate, with the object of lowering the hydrogen ion concentration. **carbon dioxide t.,** a form of (rarely used) shock therapy employed for the treatment of withdrawn psychotic patients, in which unconsciousness is induced by the administration of carbon dioxide gas by inhalation. **Chaoul t.,** short source-to-tissue distance, low-voltage roentgen therapy; see also under *tube*. **collapse t.,** treatment of pulmonary tuberculosis by operative collapse of the diseased lung. **conditioning t.,** behavior t. **convulsive t.,** treatment of mental disorders, primarily depression, by induction of convulsions. The type now almost universally used is electroconvulsive therapy (ECT), in which the convulsions are induced by electic current. In the original convulsive therapy the convulsions were induced pharmacologically, at first by pentylenetetrazol (Metrazol) and later by flurothyl (Indoklon). Formerly called *shock t.* **corrective t.,** the planning and administration of progressive physical exercise and activities most effective in improving or maintaining general physical and emotional health, through individual or group participation. **Curie t.,** treatment with a radioactive source, e.g., radium. **deep roentgen-ray t.,** treatment by x-radiations generated by at least 150 kilovolts and capable of penetrating significantly below the skin level. **deleading t.,** the use of chelating agents in the mobilization and excretion from the body of heavy metals, such as lead, radium, etc. **diathermic t.,** treatment by thermopenetration; see *diathermy*. **duplex t.,** treatment by diathermic and galvanic currents in combination, both currents being passed through the body at the same time by way of the same two electrodes. **electric convulsive t. (ECT), electric shock t. (EST),** electroconvulsive t. **electroconvulsive t. (ECT),** a treatment for mental disorders, primarily depression, in which convulsions and loss of consciousness are induced by application of low-voltage alternating current to the brain via scalp electrodes for a fraction of a second; a muscle relaxant, generally succinylcholine, is used to prevent injury during the seizure. The coma lasts about 5 minutes and is followed by an acute confusional state lasting about an hour; some memory impairment may be present for several weeks after treatment. ECT produces a therapeutic response in a majority of cases of major depression; it has also been used in schizophrenia, primarily in treatment of acute schizophrenic episodes. **electroshock t. (EST),** electroconvulsive t. **emanation t.,** treatment by ionizing radiations emitted by a radioactive source. **family t.,** group therapy of the members of a family, with exploration of family relationships and processes as potential causes of mental disorder in one or more members of the family. **fever t.,** treatment of disease by induction of high body temperature, accomplished by physical means or by injection of fever-producing vaccines. **Fliess t.,** see under *treatment*. **grid t.,** therapeutic application of ionizing radiations through a metal grid having a pattern of small, evenly spaced perforations. **group t.,** psychotherapy carried out with a group of patients or the relatives of patients or both, which includes utilization of interactions of members of the group to effect changes in maladaptive behavior of the individual members, under the guidance of a single therapist. Called also *group psychotherapy*. **heterovaccine t.,** bacterial vaccine therapy by the use of some infectious agent other than the specific one causing the disease. **high-voltage roentgen t.,** treatment by deeply penetrating x-rays generated by voltages of over 300 kilovolts. **humidification t.,** the use of air supersaturated with moisture in congestive conditions of the upper and lower respiratory tract. **hunger t.,** limotherapy. **immunization t.,** treatment with antiserum and with actively antigenic substances, e.g., vaccines. **immu-**

EXHIBIT 4

Class / Subclass / ISSUE CLASSIFICATION

PATENT NUMBER

U.S. UTILITY Patent Application

JC 906

O.I.P.E. SCANNED 5/03 Q.A. PATENT DATE

APPLICATION NO.	CONT/PRIOR	CLASS	SUBCLASS	ART UNIT	EXAMINER
09/800204	D F	424	468	1621	Barts

APPLICANTS
Ronald Muller
Sandra Malkowska
Walter Wimmer
Udo Hahn

TITLE
Controlled release tramadol formulation

PTO-2040 12/89

ISSUING CLASSIFICATION

ORIGINAL CLASS	ORIGINAL SUBCLASS	CROSS REFERENCE(S) CLASS	CROSS REFERENCE(S) SUBCLASS (ONE SUBCLASS PER BLOCK)

INTERNATIONAL CLASSIFICATION

☐ Continued on Issue Slip Inside File Jacket

☐ TERMINAL DISCLAIMER	DRAWINGS			CLAIMS ALLOWED	
	Sheets Drwg.	Figs. Drwg.	Print Fig.	Total Claims	Print Claim for O.G.
☐ The term of this patent subsequent to _____ (date) has been disclaimed.				NOTICE OF ALLOWANCE MAILED	
☐ The term of this patent shall not extend beyond the expiration date of U.S Patent. No. _____				ISSUE FEE	
				Amount Due	Date Paid
☐ The terminal ____ months of this patent have been disclaimed.				ISSUE BATCH NUMBER	

(Assistant Examiner) (Date)

(Primary Examiner) (Date)

(Legal Instruments Examiner) (Date)

WARNING:
The information disclosed herein may be restricted. Unauthorized disclosure may be prohibited by the United States Code Title 35, Sections 122, 181 and 368. Possession outside the U.S. Patent & Trademark Office is restricted to authorized employees and contractors only.

Form PTO-436A (Rev. 8/99)

FILED WITH: ☐ DISK (CRF) ☐ FICHE ☐ CD-ROM
(Attached in pocket on right inside flap)

EXHIBIT
093
4.25.08 BN

(FACE)

222.94213.CON2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Application of: Ronald B. MILLER, et al.

Serial No.: 09/800,204

Filed: March 6, 2001

For: CONTROLLED RELEASE TRAMADOL

#5/C
2/12/02
Imeua

RESPONSE TO RESTRICTION REQUIREMENT
AND PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

December 21, 2001

Dear Sirs:

In response to the Restriction requirement dated August 21, 2001, Applicants respond as follows:

Remarks

In the Office Action dated August 21, 2001, the Examiner indicated that the inventions listed as Groups I and II are distinct because "inventions I and II are related as process of making and product made... the process as claimed can be used to make other and materially different product... [therefore] restriction for examination purposes as indicated is proper."

In response to the Examiner's restriction requirement, Applicants elect claims 1-19 (Group I) directed to compositions of tramadol without traverse. This election is made without prejudice to pursuing Group II in a continuation application. Further, the Examiner is respectfully requested to enter the following amendment prior to examination.

IN THE CLAIMS

Please **cancel** claims 2-19 without prejudice.

Please **amend** claim 1 as follows:

1. (Amended) A solid controlled release oral dosage form, comprising a therapeutically effective amount of tramadol or a pharmaceutically acceptable salt thereof incorporated into a matrix, said dosage form providing a therapeutic effect for at least about 24 hours.

Please **add** new claims 21-41 as follows:

21. (New) The controlled release dosage form as claimed in claim 1, wherein said matrix is a controlled release matrix.

22. (New) The controlled release dosage form as claimed in claim 1, wherein said matrix is overcoated with a controlled release coating.

23. (New) The controlled release dosage form as claimed in claim 22, wherein said matrix is a normal release matrix.

24. (New) The controlled release dosage form as claimed in claim 22, wherein said matrix is a controlled release matrix.

25. (New) The controlled release dosage form as claimed in claim 1, containing from about 50 to 800mg of tramadol or a pharmaceutically acceptable salt thereof, calculated as the hydrochloride salt.

26. (New) The controlled release dosage form as claimed in claim 1, having a dissolution rate in-vitro when measured using the Ph. Eur. Paddle Method at 100 rpm in 900 ml 0.1N hydrochloric acid at 37°C and using UV detection at 270 nm, from about 0 to about 50% tramadol released after 1 hour; from about 0 to about 75% tramadol released after 2 hours; from about 10 to about 95% tramadol released after 4 hours; from about 35 to about 100% after 8 hours; from about 55 to about 100% tramadol released after 12 hours; from about 70 to about 100% tramadol released after 16 hours; and greater than 90% tramadol released after 24 hours, by weight.

27. (New) The controlled release dosage form as claimed in claim 1, having a dissolution rate in-vitro when measured using the Ph. Eur. Paddle Method at 100 rpm in 900 ml 0.1N hydrochloric acid at 37°C and using UV detection at 270 nm, from about 0 to about 30% tramadol released after 1 hour; from about 0 to about 40% tramadol released after 2 hours; from about 3 to about 55% tramadol released after 4 hours; from about 10 to about 65% after 8 hours; from about 20 to about 75% tramadol released after 12 hours; from about 30 to about 88% tramadol released after 16 hours; from about 50 to about 100% tramadol released after 24 hours and greater than 80% tramadol released after 36 hours, by weight.

28. (New) The controlled release dosage form as claimed in claim 1, having a dissolution rate in-vitro when measured using the Ph. Eur. Paddle Method at 100 rpm in 900 ml 0.1N hydrochloric acid at 37°C and using UV detection at 270 nm, from about 15 to about 25% tramadol released after 1 hour; from about 25 to about 35% tramadol released after 2 hours; from about 30 to about 45% tramadol released after 4 hours; from about 40 to about 60% after 8 hours; from about 55 to about 70% tramadol released after 12 hours; and from about 60 to about 75% tramadol released after 16 hours, by weight.

29. (New) The dosage form according to claim 1, which provides a t_{max} from about 3 to about 6 hours.

30. (New) The dosage form according to claim 1, which provides a W_{50} from about 10 to about 33 hours.

31. (New) A solid controlled release oral dosage form, comprising a therapeutically effective amount of tramadol or a pharmaceutically acceptable salt thereof incorporated into a matrix, said dosage form providing a therapeutic effect for at least about 12 hours.

32. (New) The controlled release dosage form as claimed in claim 31, wherein said matrix is a controlled release matrix.

33. (New) The controlled release dosage form as claimed in claim 31, wherein said matrix is overcoated with a controlled release coating.

34. (New) The controlled release dosage form as claimed in claim 33, wherein said matrix is a normal release matrix.

35. (New) The controlled release dosage form as claimed in claim 33, wherein said matrix is a controlled release matrix.

36. (New) The controlled release dosage form as claimed in claim 31, containing from about 50 to 400mg of tramadol or a pharmaceutically acceptable salt thereof, calculated as the hydrochloride salt.

37. (New) The controlled release dosage form as claimed in claim 31, having a dissolution rate in vitro when measured using the Ph. Eur. Paddle Method at 100 rpm in 900 ml 0.1N hydrochloric acid at 37°C and using UV detection at 270 nm, from about 0 to about 50% tramadol released after 1 hour; from about 0 to about 75% tramadol released after 2 hours; from about 3 to about 95% tramadol released after 4 hours; from about 10 to about 100% after 8 hours; from about 20 to about 100% tramadol released after 12 hours; from about 30 to about 100% tramadol released after 16 hours; from about 50 to about 100% tramadol released after 24 hours; and greater than 80% tramadol released after 36 hours, by weight.

38. (New) The controlled release dosage form as claimed in claim 31, having a dissolution rate in vitro when measured using the Ph. Eur. Paddle Method at 100 rpm in 900 ml 0.1N hydrochloric acid at 37°C and using UV detection at 270 nm, from about 20 to about 50% tramadol released after 1 hour; from about 40 to about 75% tramadol released after 2 hours; from about 60 to about 95% tramadol released after 4 hours; from about 80 to about 100% after 8 hours; and from about 90 to about 100% tramadol released after 12 hours, by weight.

39. (New) The controlled release dosage form as claimed in claim 31, having a dissolution rate in vitro when measured using the Ph. Eur. Paddle Method at 100 rpm in 900 ml 0.1N hydrochloric acid at 37°C and using UV detection at 270 nm, from about 5 to about 50% tramadol released after 1 hour; from about 10 to about 75% tramadol released after 2 hours; from about 20 to about 95% tramadol released after 4 hours; from about 40 to about 100% after 8 hours; more than 50% tramadol released after 12 hours; more than 75% tramadol released after 18 hours; and more than 80% tramadol released after 24 hours, by weight.

40. (New) The dosage form according to claim 31, which provides a t_{max} from about 1.5 to about 8 hours.

41. (New) A dosage form according to claim 31, which provides a W_{50} from about 7 to about 16 hours.

CONCLUSION

Claims 1 and 21-41 are pending. Claim 20 has been withdrawn and claims 2-19 have been canceled without prejudice. Claim 1 has been amended and claims 21-41 have been added. Support for claim 1 can be found in the specification on page 1, paragraphs 3-5; and page 6, paragraph 3. Support for claims 21-25 can be found on page 6, paragraphs 1-2. Support for claim 26 can be found on page 3, table 3. Support for claim 27 can be found on page 4, table 4. Support for claims 28-30 can be found on page 5, paragraph 3. Support for claims 31-36 can be found on page 6, paragraphs 1and 3. Support for claim 37 can be found on page 2, table 1. Support for claim 38 can be found on page 3, table 2. Support for claim 39 can be found on page 4, last paragraph. Support for claims 40 and 41 can be found on page 5, paragraphs 2 and 3. Applicants respectfully submit that no new matter has been added by virtue of these amendments.

A check in the amount of $36.00 is enclosed to cover the fee under 37 C.F.R. §1.16(c) for additional claims added. It is believed that no fees are due under 37 C.F.R. 1.17 (extension fees) as the Office Action mailed August 21, 2001 did not set forth any shortened statutory period for reply. If it is determined that a petition for extension and extension fees are required, Applicants respectfully request that this communication be considered as a request for such an extension and the Assistant Commissioner is hereby authorized to charge said fee or credit any overpayment to Deposit Account No. 50-0552.

An early and favorable action on the merits is earnestly solicited.

Respectfully submitted,
DAVIDSON, DAVIDSON & KAPPEL, LLC

By: _____
Robert J. Paradiso
Reg. No. 41,240

Davidson, Davidson & Kappel, LLC
485 Seventh Avenue, 14th Floor
New York, New York 10018
(212) 736-1940

Marked-Up Amended Claims

1. (Amended) A solid controlled release [preparation] oral dosage form, comprising a therapeutically effective amount of tramadol or a pharmaceutically acceptable salt thereof [for oral administration] incorporated into a matrix, said dosage form providing a therapeutic effect for at least about 24 hours.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/800,204	03/06/2001	Ronald Brown Miller	222.94213.CON2	1587

23280 7590 04/23/2002

DAVIDSON, DAVIDSON & KAPPEL, LLC
485 SEVENTH AVENUE, 14TH FLOOR
NEW YORK, NY 10018

EXAMINER	
BARTS, SAMUEL A	

ART UNIT	PAPER NUMBER
1621	6

DATE MAILED: 04/23/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/800,204	Applicant(s) MILLER ET AL	
	Examiner Samuel Barts	Art Unit 1621	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 January 2002* .

2a)☐ This action is FINAL. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 20-41* is/are pending in the application.

4a) Of the above claim(s) *20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 21-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign languag provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I claims 1-19 and 21-41 in Paper No. 5 is acknowledged.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> **(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.**

3. Claims 1-19 and 21-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Raffa et al (Caplus 1992:120745, J. Phamacol. Exp. Ther. 1992, 260 (1), 275-85) in view of Bondi (EP 0147780).

Raffa et al teach the use of Tramadol hydrochloride as a pain medicament with opioid and nonopioid properties. The reference teaches Tramadol as a pain medicine working from two different pathways. The instant claimed invention is drawn to oral composition of Tramadol with controlled release features. Some of the claims specifically recite a dissolution rate that is measured by a specific test. The instant claimed invention differs from the prior art by requiring a controlled release composition. The secondary reference of Bondi teaches a controlled release method for a variety of compounds of which Tramadol is listed as an example (see page 7 lines 31-34).

It would have been obvious to one of ordinary skill in the art at the time that applicant's invention was made to have used the controlled release method taught in

Bondi for making an oral composition of Tramadol. Note that Bondi teaches a matrix controlled release system. See for example page 4 lines 1-6. Such a modification would have been obvious because a controlled release composition is the standard and most common way of administering pain medicaments. Thus a skilled artisan preparing the Tramadol for human use would look to use standard controlled release methods such as taught in Bondi.

The claims drawn to specific amounts, specific dosage forms, specific dissolution rates etc., are all obvious since a skilled artisan would reasonably be expected to tweak the controlled release form of Tramadol to meet a variety of needs. For example it is well known that over the counter pain medicines come in countless dosage forms and most come in different controlled release time factors. Pain medicine is typically given in different dosage form depending on such factors as; a) age of patient, b) adult or child c) size and weight of patient, d) particular pain being treated etc.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Barts whose telephone number is 703-308-4630. The examiner can normally be reached on M-F between 6:30am-3:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 703-308-1235. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-3081235.

Samuel Barts
Primary Examiner
Art Unit 1621

s.b.
April 21, 2002

#3
11/1/02
Timely

222.94213.CON2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner: Samuel A. BARTS Art Unit: 1621

In re: Application of: Ronald B. MILLER, et al.

Serial No.: 09/800,204

Filed: March 6, 2001

For: **CONTROLLED RELEASE TRAMADOL**

RESPONSE UNDER 37 C.F.R. § 1.111

Assistant Commissioner for Patents
Washington, D.C. 20231

October 23, 2002

Sirs:

In response to the Office Action mailed April 23, 2002, Applicants respectfully submit the following remarks:

REJECTION UNDER 35 U.S.C. § 103(a):

In the Office Action, the Examiner rejected claims 1-19 and 21-41 under 35 U.S.C. § 103(a) as being unpatentable over Raffa *et al.* ((Caplus 1992:120745, J. Pharmacol. Exp. Ther. 1992, 260 (1), 275-85)) in view of EP 0147780 to Bondi ("the Bondi patent"). The Examiner stated that "Raffa et al teach the use of Tramadol hydrochloride as a pain medicament with opioid and nonopioid properties... The instant claimed invention differs from the prior art by requiring a controlled release composition... The secondary reference to Bondi teaches a controlled release method for a variety of compounds of which Tramadol is listed as an example... It would have been obvious to one of ordinary skill in the art at the time the invention was made to have used the controlled release method taught in Bondi for making an oral composition of Tramadol... The claims drawn to specific amounts, specific dosage forms,

specific dissolution rates etc., are all obvious since a skilled artisan would reasonably be expected to tweak the controlled release form of Tramadol [of Bondi] to meet a variety of needs"

These rejections are respectfully traversed. At the very least, it is respectfully submitted that the Raffa reference and the Bondi patent are not properly combinable. According to the abstract of the Raffa reference, tramadol was administered to rats by intracerebral-ventricular and intrathecal administration. The Raffa reference does not contemplate controlled release oral dosage forms. In contrast, the Bondi reference purports to describe controlled release drug delivery systems of a plethora of active agents and does not contemplate immediate release dosage forms. Accordingly, one skilled in the art would not be motivated to combine the Raffa reference with the Bondi reference.

Further, the Bondi reference includes tramadol in an exhaustive list of possible active agents which can be included in the drug delivery device described therein. Due to the large scope of listed compounds in this reference, one skilled in the art would not view this reference as teaching tramadol controlled release formulations. Accordingly, one skilled in the art would not combine the Bondi reference with the Raffa reference which is specifically directed to tramadol.

Even assuming arguendo that these references were properly combinable, it is respectfully submitted that one skilled in the art would not arrive at the present invention based on the combination of the cited references. The Examiner is directed to independent claims 1 and 31 which are as follows:

1. *A solid controlled release oral dosage form, comprising a therapeutically effective amount of tramadol or a pharmaceutically acceptable salt thereof incorporated into a matrix such that said dosage form provides a therapeutic effect for at least about 24 hours. (Emphasis added)*

31. *A solid controlled release oral dosage form, comprising a therapeutically effective amount of tramadol or a pharmaceutically acceptable salt thereof incorporated into a matrix such that said dosage form provides a therapeutic effect for at least about 12 hours. (Emphasis added)*

As recited in the present claims, the present invention is directed to oral dosage forms comprising tramadol which provide specific pharmacokinetic parameters, i.e., a therapeutic effect for at least about 12 hours or 24 hours. The Bondi reference merely states that the drug delivery devices described therein are useful for "dispensing a composition of matter at a controlled rate for a prolonged period of time." The Bondi reference does not teach that the formulations described therein provide a therapeutic effect for at least about 12 hours or 24 hours as recited in the present claims. Furthermore, the Bondi reference does not suggest that the formulations described therein can be modified to attain the claimed pharmacokinetic parameters. Accordingly, one skilled in the art would not arrive at the present invention based on a combination of the Raffa and Bondi references.

CONCLUSION

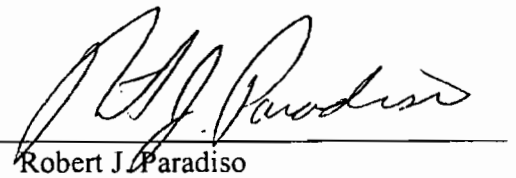
Claims 1 and 21-41 are pending. In view of the arguments made, Applicants respectfully submit that the pending claims are in condition for allowance. An early and favorable action on the merits is earnestly solicited.

A check in the amount of $920.00 is enclosed for the fee for a three-month extension of time. If it is determined that any additional fees are due or that any fees have been overpaid, the Commissioner for Patents is hereby authorized to charge said fees or credit any overpayment to Deposit Account No. 50-0552.

In addition, Applicants submit herewith a Supplemental Information Disclosure Statement and Attachments A-D. Attachments A-D were previously submitted during the prosecution of the parent case, U.S. Serial No, 08/449,772, now U.S. Patent No. 6,326,027.

Respectfully submitted,

DAVIDSON, DAVIDSON & KAPPEL, LLC

By: 

Robert J Paradiso
Reg. No. 41, 240

Davidson, Davidson & Kappel, LLC
485 Seventh Avenue, 14th Floor
New York, New York 10018
(212) 736-1940

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/800,204	03/06/2001	Ronald Brown Miller	222.94213.CON2	1587

23280 7590 01/14/2003

DAVIDSON, DAVIDSON & KAPPEL, LLC
485 SEVENTH AVENUE, 14TH FLOOR
NEW YORK, NY 10018

EXAMINER	
BARTS, SAMUEL A	

ART UNIT	PAPER NUMBER
1621	9

DATE MAILED: 01/14/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/800,204	MILLER ET AL.	
	Examiner	Art Unit	
	Samuel A Barts	1621	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for R ply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 October 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 20-41* is/are pending in the application.

4a) Of the above claim(s) *20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 21-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Information Disclosure Statement

1. The information disclosure statement filed October 29,2002 fails to comply with 37 CFR 1.98(a)(1), which requires a list of all patents, publications, or other information submitted for consideration by the Office. It has been placed in the application file, but the information referred to therein has not been considered.

Response to Arguments

2. Applicant's arguments filed October 29,2002 have been fully considered but they are not persuasive.

Argument 1: The references are not properly combinable. Applicant argues that the Raffa et al reference fails to contemplate a controlled release oral dosage form. Applicant further adds that the Bondi reference teaches controlled release oral dosage forms but recites tramadol among a laundry list of other pharmaceuticals. Applicant then concludes that there would be no motivated to combine these references.

Examiner Response: The Raffa et al reference of course did not teach controlled released dosage, because if it did the reference would have anticipated the claimed invention. Therefore, the real question is whether one of ordinary skill in the art having a compound with a pharmaceutical property would be motivated to look for a controlled method of administering said pharmaceutical.

The administering of pharmaceutical via a controlled means is fundamental. Even the general public is exceedingly aware of a time factor when taking medicines from antihistamines, cold medicaments and even vitamins. A skilled artisan is aware of making compositions that produce these time factors for medicines. Hence, once a compound has been recognized as having a beneficial pharmaceutical property, one of ordinary skill in the art would look for methods of controlled release of that pharmaceutical. Since, the secondary reference of Bondi recites controlled release methods and list tramadol one would be motivated to use the teaching of Bondi. The fact that a large laundry list of compounds is recited does not minimize the teaching of this reference. In fact it actually strengthens the suggestion that controlled release methods are well known and that they can be used for a wide variety of pharmaceuticals. Which is the position the Examiner has taken.

Argument 2: Applicant puts forth the position that even if the combination is proper there is no suggestion of making a dosage form for at least about 12 hours or 24 hours.

Examiner Response: The dosage form of medicaments is extremely well known. Again even the general public is aware of taking medicaments based on how long they will last. Therefore, one of ordinary skill in the art would be motivated

to modify the dosage form to standard time frames. 4, 8, 12 and 24 hrs are recognized standard time frames for pharmaceuticals. A 24 hrs dosage form simply means once a day. A 12 hrs dosage form means twice a day.

The rejection is being maintained.

Claim Rejections - 35 USC § 103

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Claims 1 and 21-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Raffa et al in view of Bondi. For reasons see previous office action and above arguments.

Conclusion

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In

no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel A Barts whose telephone number is 703-308-4630. The examiner can normally be reached on 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johan Richter can be reached on 308-1235. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Samuel A Barts
Primary Examiner
Art Unit 1621

s.b.
January 12, 2003

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/800,204	03/06/2001	Ronald Brown Miller	222.94213.CON2	1587

23280 7590 10/21/2003

DAVIDSON, DAVIDSON & KAPPEL, LLC
485 SEVENTH AVENUE, 14TH FLOOR
NEW YORK, NY 10018

EXAMINER	
BARTS, SAMUEL A	
ART UNIT	**PAPER NUMBER**
1621	14

DATE MAILED: 10/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/800,204	MILLER ET AL.	
	Examiner	Art Unit	
	Samuel A Barts	1621	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1,20 and 42-62 is/are pending in the application.

4a) Of the above claim(s) 20 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) 1 and 42-62 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 13 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 103

Claim Objections

1. The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Claims 2-19 were canceled in the response to election requirement filed January 18/20002. In this same response, claims 21-41 were added. However, previously on March 6, 2001 original numbered claims 21-41 were cancelled. Therefore the newly added claims of January 18 2002 should have been numbered 42-62.

Misnumbered claim21-41 have been renumbered to 42-62

Status of Claims

2. Claims 1 and 42-62 are rejected

Claim 20 is withdrawn from consideration.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1 and 42-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Raffa et al in view of Bondi. For reasons see previous office actions of 4/23/02 and 1/14/03.

Conclusion

5. This is a RCE of applicant's earlier Application No. 09/800,204. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH

shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel A Barts whose telephone number is 703-308-4630. The examiner can normally be reached on 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johan Richter can be reached on 308-1235. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Samuel A Barts
Primary Examiner
Art Unit 1621

s.b.

222.94213CON2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner: Samuel A. BARTS Art Unit: 1621

In re: Application of: Ronald B. MILLER, et al.

Serial No.: 09/800,204

Filed: March 6, 2001

For: **CONTROLLED RELEASE TRAMADOL**

RESPONSE UNDER 37 C.F.R. § 1.116

Mail Stop: AF
Commissioner for Patents
P.O. Box 1450
Arlington, VA 22313-1450

April 21, 2004

I. INTRODUCTORY COMMENTS

Sirs:

In response to the final Office Action mailed October 21, 2003, Applicants respectfully submit the following response:

Amendments to the claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 6.

II. LISTING OF THE CLAIMS

Claim 1. (Previously presented) A solid controlled release oral dosage form, comprising a therapeutically effective amount of tramadol or a pharmaceutically acceptable salt thereof incorporated into a matrix, said dosage form providing a therapeutic effect for at least about 24 hours.

Claim 42. (Previously presented) The controlled release dosage form as claimed in claim 1, wherein said matrix is a controlled release matrix.

Claim 43. (Previously presented) The controlled release dosage form as claimed in claim 1, wherein said matrix is overcoated with a controlled release coating.

Claim 44. (Currently amended) The controlled release dosage form as claimed in claim 43 ~~22~~, wherein said matrix is a normal release matrix.

Claim 45. (Currently amended) The controlled release dosage form as claimed in claim 43 ~~22~~, wherein said matrix is a controlled release matrix.

Claim 46. (Previously presented) The controlled release dosage form as claimed in claim 1, containing from about 50 to 800mg of tramadol or a pharmaceutically acceptable salt thereof, calculated as the hydrochloride salt.

Claim 47. (Previously presented) The controlled release dosage form as claimed in claim 1, having a dissolution rate in-vitro when measured using the Ph. Eur. Paddle Method at 100 rpm in 900 ml 0.1N hydrochloric acid at 37°C and using UV detection at 270 nm, from about 0 to about 50% tramadol released after 1 hour; from about 0 to about 75% tramadol released after 2 hours; from about 10 to about 95% tramadol released after 4 hours; from about 35 to about 100% after 8 hours; from about 55 to about 100% tramadol released after 12 hours; from about 70 to about 100% tramadol released after 16 hours; and greater than 90% tramadol released after 24 hours, by weight.

Claim 48. (Previously presented) The controlled release dosage form as claimed in claim 1, having a dissolution rate in-vitro when measured using the Ph. Eur. Paddle Method at 100 rpm in 900 ml 0.1N hydrochloric acid at 37°C and using UV detection at 270 nm, from about 0 to about 30% tramadol released after 1 hour; from about 0 to about 40% tramadol released after 2 hours; from about 3 to about 55% tramadol released after 4 hours; from about 10 to about 65% after 8 hours; from about 20 to about 75% tramadol released after 12 hours; from about 30 to about 88% tramadol released after 16 hours; from about 50 to about 100% tramadol released after 24 hours and greater than 80% tramadol released after 36 hours, by weight.

Claim 49. (Previously presented) The controlled release dosage form as claimed in claim 1, having a dissolution rate in-vitro when measured using the Ph. Eur. Paddle Method at 100 rpm in 900 ml 0.1N hydrochloric acid at 37°C and using UV detection at 270 nm, from about 15 to about 25% tramadol released after 1 hour; from about 25 to about 35% tramadol released after 2 hours; from about 30 to about 45% tramadol released after 4 hours; from about 40 to about 60% after 8 hours; from about 55 to about 70% tramadol released after 12 hours; and from about 60 to about 75% tramadol released after 16 hours, by weight.

Claim 50. (Previously presented) The dosage form according to claim 1, which provides a t_{max} from about 3 to about 6 hours.

Claim 51. (Previously presented) The dosage form according to claim 1, which provides a W_{50} from about 10 to about 33 hours.

Claim 52. (Previously presented) A solid controlled release oral dosage form, comprising a therapeutically effective amount of tramadol or a pharmaceutically

acceptable salt thereof incorporated into a matrix, said dosage form providing a therapeutic effect for at least about 12 hours.

Claim 53. (Currently amended) The controlled release dosage form as claimed in claim 52 ~~31~~, wherein said matrix is a controlled release matrix.

Claim 54. (Currently amended) The controlled release dosage form as claimed in claim 52 ~~31~~, wherein said matrix is overcoated with a controlled release coating.

Claim 55. (Currently amended) The controlled release dosage form as claimed in claim 54 ~~33~~, wherein said matrix is a normal release matrix.

Claim 56. (Currently amended) The controlled release dosage form as claimed in claim 54 ~~33~~, wherein said matrix is a controlled release matrix.

Claim 57. (Currently amended) The controlled release dosage form as claimed in claim ~~31~~ 52, containing from about 50 to 400mg of tramadol or a pharmaceutically acceptable salt thereof, calculated as the hydrochloride salt.

Claim 58. (Currently amended) The controlled release dosage form as claimed in claim ~~31~~ 52, having a dissolution rate in vitro when measured using the Ph. Eur. Paddle Method at 100 rpm in 900 ml 0.1N hydrochloric acid at 37°C and using UV detection at 270 nm, from about 0 to about 50% tramadol released after 1 hour; from about 0 to about 75% tramadol released after 2 hours; from about 3 to about 95% tramadol released after 4 hours; from about 10 to about 100% after 8 hours; from about 20 to about 100% tramadol released after 12 hours; from about 30 to about 100% tramadol released after 16 hours; from about 50 to about 100% tramadol released after 24 hours; and greater than 80% tramadol released after 36 hours, by weight.

Claim 59. (Currently amended) The controlled release dosage form as claimed in claim ~~31~~ 52, having a dissolution rate in vitro when measured using the Ph. Eur. Paddle Method at 100 rpm in 900 ml 0.1N hydrochloric acid at 37°C and using UV detection at 270 nm, from about 20 to about 50% tramadol released after 1 hour; from about 40 to about 75% tramadol released after 2 hours; from about 60 to about 95% tramadol released after 4 hours; from about 80 to about 100% after 8 hours; and from about 90 to about 100% tramadol released after 12 hours, by weight.

Claim 60. (Currently amended) The controlled release dosage form as claimed in claim ~~31~~ 52, having a dissolution rate in vitro when measured using the Ph. Eur. Paddle Method at 100 rpm in 900 ml 0.1N hydrochloric acid at 37°C and using UV detection at 270 nm, from about 5 to about 50% tramadol released after 1 hour; from about 10 to about 75% tramadol released after 2 hours; from about 20 to about 95% tramadol released after 4 hours; from about 40 to about 100% after 8 hours; more than 50% tramadol released after 12 hours; more than 75% tramadol released after 18 hours; and more than 80% tramadol released after 24 hours, by weight.

Claim 61. (Currently amended) The dosage form according to claim ~~31~~ 52, which provides a t_{max} from about 1.5 to about 8 hours.

Claim 62. (Currently amended) A dosage form according to claim ~~31~~ 52, which provides a W_{50} from about 7 to about 16 hours.

III. REMARKS/ARGUMENTS

Claims 1 and 42-62 are pending. The claims have been amended in order to correct dependencies due to the renumbering of the previously submitted claims.

Rejection Under 35 U.S.C. § 103(a)

In the Office Action, the Examiner rejected claims 1 and 42-62 under 35 U.S.C. § 103(a) as being unpatentable over Raffa *et al.* ((Caplus 1992:120745, J. Pharmacol. Exp. Ther. 1992, 260 (1), 275-85)) in view of EP 0147780 to Bondi ("the Bondi reference"). The Examiner's rejection was based on his previous Office Actions mailed April 23, 2002 and January 14, 2003. In the previous Office Actions the Examiner stated that "Raffa et al teach the use of Tramadol hydrochloride as a pain medicament with opioid and nonopioid properties... The instant claimed invention differs from the prior art by requiring a controlled release composition... The secondary reference to Bondi teaches a controlled release method for a variety of compounds of which Tramadol is listed as an example... It would have been obvious to one of ordinary skill in the art at the time the invention was made to have used the controlled release method taught in Bondi for making an oral composition of Tramadol... The claims drawn to specific amounts, specific dosage forms, specific dissolution rates etc., are all obvious since a skilled artisan would reasonably be expected to tweak the controlled release form of Tramadol [of Bondi] to meet a variety of needs"

The Examiner's rejection is respectfully traversed.

Independent claim 1 recites: "*a solid controlled release oral dosage form, comprising a therapeutically effective amount of tramadol or a pharmaceutically acceptable salt thereof incorporated into a matrix, said dosage form providing a therapeutic effect for at least about 24 hours.*" (Emphasis Added)

Independent claim 52 recites: "*a solid controlled release oral dosage form, comprising a therapeutically effective amount of tramadol or a pharmaceutically acceptable salt thereof incorporated into a matrix, said dosage form providing a therapeutic effect for at least about 12 hours.*" (Emphasis Added)

The Bondi reference describes controlled release compositions for release of drugs through a rate limiting barrier by coating a formulation with a coating comprising polyvinyl alcohol, which serves as a membrane or barrier film which selectively permits passage of the drug. Although the specification of this reference states that the drug may be dispersed homogeneously throughout a matrix composed of polyvinyl alcohol, this embodiment is not exemplified. All of the examples are directed to formulations comprising film coatings which comprise polyvinyl alcohol.

Tramadol limitation

The Bondi reference describes that the reference is suitable for use with, but not limited to, a large genus of possible active agents. This genus is listed in the Bondi reference starting on page 5, line 24 to page 9, line 16. This exhaustive genus includes many hundreds of compounds Accordingly, the recitation of tramadol (page 7, line 30) is merely a single species of the large genus described in the Bondi reference.

It is respectfully submitted that one skilled in the art would not be motivated to select the particular claimed species (i.e. tramadol) from the large genus disclosed on pages 5-9 of the Bondi reference and combine this reference with the Raffa reference. In support of this position, it is respectfully submitted that with respect to Bondi, (i) the size of the genus is not sufficiently small as to render each member of the genus inherently disclosed, (ii) the reference does not expressly teach a particular reason to select the claimed species; and (iii) there is no teaching of structural similarity in the reference. A discussion of these points follows:

(i) The size of the genus is not sufficiently small as to render each member of the genus inherently disclosed

The fact that a claimed species is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness. *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994). Some motivation to select the

claimed species or subgenus must be taught by the prior art. See e.g., *In re Deuel*, 51 F.3d at 1558-59, 34 USPQ2d at 1215.

It has been held that a prior art genus containing only 20 compounds inherently anticipated a claimed species within the genus. *In re Petering*, 301 F.2d 676,681, 133 USPQ 275, 280 (CCPA 1962). As presented above, the Bondi reference describes a genus including many hundreds of compounds. It is respectfully submitted that the Bondi reference does not render obvious each and every individual species (e.g. tramadol) which falls within their broad genus, based on the size of the genus. Therefore, one skilled in the art would not select tramadol from the Bondi reference and combine the Raffa reference.

(ii) The reference does not expressly teach a particular reason to select the claimed species

If a prior art reference expressly teaches a particular reason to select the claimed species, the Examiner should point out the express disclosure which would have motivated one of ordinary skill in the art to select the claimed species. See MPEP 8th Edition, 1st revision 2144.08 II (A)(4)(B). It is respectfully submitted that the only recitation of tramadol in the Bondi reference is embedded within a large genus. Accordingly, the Bondi reference does not expressly teach a particular reason to select tramadol from the plethora of other possible species in the genus of the reference and combine this reference with the Raffa reference.

(iii) There is no teaching of structural similarity in the reference

If a preferred species is structurally similar to that claimed, its disclosure may motivate one of ordinary skill in the art to choose the claimed species from the genus. See, e.g., *In re Dillon*, 919 F.2d at 693, 696, 16 USPQ2d at 1901, 1904. It is noted that the preferred active agents exemplified in the Bondi reference are L-dopa and timolol maleate in Examples 1 and 2 respectively.

It is respectively submitted that L-dopa (3-hydroxy-L-tyrosine, an anti-parkinsonian) and timolol maleate ((S)-1-[(1,1-dimethylethyl)amino]-3-[[4-(4-morpholinyl)- 1,2,5-thiadiazol -3 -yl]oxy]-2-propanol maleate, a beta-blocker) are not similar in structure to tramadol (i.e., (±)-trans-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol). Accordingly, as the Bondi reference does not teach any preferred species which have structural similarity to tramadol, there is no motivation therein to one skilled in the art to select tramadol from the large genus therein and combine this reference with the Raffa reference.

Further, any teaching or suggestion in the reference of a preferred species that is significantly different in structure from the claimed species weigh against selecting the later selected species. Baird, 16 F.3d 382-83, 29 USPQ2d 1552 (Fed. Cir. 1994). Accordingly, the examples of the Bondi reference directed to compounds that are not structurally similar to tramadol is further evidence that one skilled in the art would not be motivated to select tramadol from the genus described therein.

12 hour and 24 hour limitations

The Bondi reference does not teach, hint or suggest that the delivery systems described therein provide a therapeutic effect of the active agent for a period of at least about 12 or about 24 hours as claimed in independent claims 52 and 1, respectively. There are no clinical trials reported therein, there are no indications that the dosage forms described therein were ever administered to human subjects, and there is no teaching or suggestion of any desired pharmacokinetic parameters reported in Bondi. Therefore, a combination of the Raffa reference with the Bondi reference would not result in a dosage form which provides a therapeutic effect of the active agent for a period of at least about 12 or about 24 hours.

In addition, the Examiner has not provided any motivation to obtain a dosage form comprising tramadol which provides a therapeutic effect for a period of at least about 12 or about 24 hours. It is noted that the factual question of motivation is material to patentability, and cannot be resolved on subjective belief and unknown authority and that the Examiner must explain reasons why one of ordinary skill in the art would have

been motivated to select references and to combine them to render the claimed invention obvious. See *In Re Lee*, 61 USPQ2d 1430, (Fed. Cir. 2002).

It is respectfully submitted that the Examiner has not provided any objective authority (e.g., a secondary reference) in combination with the Raffa and Bondi references which would provide motivation to one skilled in the art to arrive at the claimed pharmacokinetic parameters (i.e., a therapeutic effect of tramadol for at least 12 or 24 hour).

In fact, it is respectfully submitted that the formulations described in the Bondi reference do not exhibit or enable 12 to 24 hour controlled release dosage forms. This is supported by the enclosed Declaration (Exhibit A) of Dr. Sandra Malkowska, which was previously submitted during the prosecution of the parent case, U.S. Patent Application Serial No. 08/241,129, filed May 10, 1994, now U.S. Patent No. 5,591,452 and the corresponding European case, European Patent Application No. 94303128.6, now EP 0 624 366. Ms. Malkowska is one of the named inventors in the presently claimed invention.

Exhibit A demonstrates that practical attempts on behalf of inventor Malkowska to produce sustained release compositions in accordance with the teachings of the Bondi reference resulted in a product which released greater than 90% active agent after 2 hours. Tablets were prepared using the formula and process of Example 1 of the Bondi reference, but replacing the L-dopa with tramadol hydrochloride. The dissolution rates obtained from Experiments 1 and 2 were as follows:

Table I

	Product- Experiment 2	Product- Experiment 1
Hour		
1	88	59
2	98	91
3	99	102
4	99	107
5	99	109
6	99	110

As demonstrated above, the tramadol formulations of the Malkowska declaration resulted in products which resulted in 88 % tramadol released at 1 hour and 91 % tramadol released at 2 hours. Although in-vitro results cannot predict in-vivo results, in-vitro parameters are used as an indication of what formulations would be suitable for further testing. It is respectfully submitted that one skilled in the art would not subject the above formulations to further testing as there is no indication that such formulations would be suitable for 12 or 24 hour formulations, based on the in-vitro result of 88 % tramadol released at 1 hour and 91 % tramadol released at 2 hours for the experimental formulations.

Accordingly, it is respectfully submitted that the Bondi reference does not exhibit or enable formulations which provide a therapeutic effect for at least 12 or 24 hours as presently claimed. Therefore, a combination of the Raffa reference with the Bondi reference would not result in a dosage form which provides a therapeutic effect of the active agent for a period of at least about 12 or about 24 hours.

IV. CONCLUSION

It is now believed that the above-referenced rejections have been obviated and it is respectfully requested that the rejections be withdrawn. It is believed that all claims are now in condition for allowance.

Enclosed is a check in the amount of $1280.00 to cover the fee for the three-month extension of time and Notice of Appeal.

An early and favorable action on the merits is earnestly solicited.

Respectfully submitted,
DAVIDSON, DAVIDSON & KAPPEL, LLC

By: _____
Robert J. Paradiso
Reg. No. 41,240

Davidson, Davidson & Kappel, LLC
485 Seventh Avenue, 14th Floor
New York, New York 10018
(212) 736-1940

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/800,204	03/06/2001	Ronald Brown Miller	222.94213.CON2	1587

23280 7590 09/13/2004

DAVIDSON, DAVIDSON & KAPPEL, LLC
485 SEVENTH AVENUE, 14TH FLOOR
NEW YORK, NY 10018

EXAMINER	
BARTS, SAMUEL A	
ART UNIT	**PAPER NUMBER**
1621	

DATE MAILED: 09/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/800,204	MILLER ET AL.	
	Examiner	Art Unit	
	Samuel A Barts	1621	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *6/25/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 42-62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 42-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

1. Applicant's arguments filed 4/23/2004 have been fully considered but they are not persuasive. Applicant has attacked the Bondi et al reference as being to broad to render obvious the instant claims. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). To this degree, note that applicant has selectively attacked the Bondi reference. The examiner has not rejected the claims over the Bondi et al reference. The rejection is over Raffa et al in view of Bondi. The In re Baird analysis of the Bondi et al reference is inappropriate here.

The rejection is being maintained.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 and 42-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Raffa et al in view of Bondi. For reasons see office action dated 4/23/02 and supporting arguments of final office actions dated 1/14/03 and 10/21/03.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel A Barts whose telephone number is 571-272-2870. The examiner can normally be reached on 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Samuel A Barts
Primary Examiner
Art Unit 1621

sb

222.94213CON2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner: Samuel A. BARTS Art Unit: 1621

In re: Application of: Ronald B. MILLER, et al.

Serial No.: 09/800,204

Filed: March 6, 2001

For: **CONTROLLED RELEASE TRAMADOL**

AMENDEMNT and STATEMENT OF SUBSTANCE OF INTERVIEW UNDER 37 CFR §1.133

Commissioner for Patents
P.O. Box 1450
Arlington, VA 22313-1450

January 12, 2005

Sir:

In response to the Office Action mailed September 13, 2004, Applicants respectfully submit the following response:

I. INTRODUCTORY COMMENTS

Listing of claims begins on page 2 of this paper.

Remarks/Arguments begin on page 7.

01/18/2005 TLUU11 00000022 09800204
01 FC:1202 250.00 OP

II. LISTING OF THE CLAIMS

The claims have not been amended. This listing of claims is being provided for the Examiner's convenience.

Claim 1.(currently amended): A solid controlled release oral dosage form, comprising,

a therapeutically effective amount of tramadol or a pharmaceutically acceptable salt thereof incorporated into a normal release matrix,

said matrix overcoated with a controlled release coating comprising a polymethacrylate or a water insoluble cellulose,

said dosage form providing a therapeutic effect for at least about 24 hours.

Claim 42.(currently amended): The controlled release dosage form as claimed in claim 1, wherein said ~~matrix is a~~ controlled release ~~matrix~~ coating comprises a polymethacrylate.

Claim 43.(currently amended): The controlled release dosage form as claimed in claim 1, wherein said ~~matrix is overcoated with a~~ controlled release coating comprises a water insoluble cellulose.

Claim 44.(currently amended): The controlled release dosage form as claimed in claim 42 ~~43~~, wherein said ~~matrix is a normal release matrix~~ controlled release coating further comprises a water soluble cellulose.

Claim 45.(currently amended): The controlled release dosage form as claimed in claim 43, wherein said ~~matrix is a controlled release matrix~~ controlled release coating further comprises a polyvinylpyrrolidone.

Claim 46.(previously presented): The controlled release dosage form as claimed in claim 1, containing from about 50 to 800mg of tramadol or a pharmaceutically acceptable salt thereof, calculated as the hydrochloride salt.

Claim 47.(previously presented): The controlled release dosage form as claimed in claim 1, having a dissolution rate in-vitro when measured using the Ph. Eur. Paddle Method at 100 rpm in 900 ml 0.1N hydrochloric acid at 37°C and using UV detection at 270 nm, from about 0 to about 50% tramadol released after 1 hour; from about 0 to about 75% tramadol released after 2 hours; from about 10 to about 95% tramadol released after 4 hours; from about 35 to about 100% after 8 hours; from about 55 to about 100% tramadol released after 12 hours; from about 70 to about 100% tramadol released after 16 hours; and greater than 90% tramadol released after 24 hours, by weight.

Claim 48.(previously presented): The controlled release dosage form as claimed in claim 1, having a dissolution rate in-vitro when measured using the Ph. Eur. Paddle Method at 100 rpm in 900 ml 0.1N hydrochloric acid at 37°C and using UV detection at 270 nm, from about 0 to about 30% tramadol released after 1 hour; from about 0 to about 40% tramadol released after 2 hours; from about 3 to about 55% tramadol released after 4 hours; from about 10 to about 65% after 8 hours; from about 20 to about 75% tramadol released after 12 hours; from about 30 to about 88% tramadol released after 16 hours; from about 50 to about 100% tramadol released after 24 hours and greater than 80% tramadol released after 36 hours, by weight.

Claim 49.(previously presented): The controlled release dosage form as claimed in claim 1, having a dissolution rate in-vitro when measured using the Ph. Eur. Paddle Method at 100 rpm in 900 ml 0.1N hydrochloric acid at 37°C and using UV detection at 270 nm, from about 15 to about 25% tramadol released after 1 hour; from about 25 to about 35% tramadol released after 2 hours; from about 30 to about 45% tramadol released after 4 hours; from about 40 to about 60% after 8 hours; from about 55 to about 70% tramadol released after 12 hours; and from about 60 to about 75% tramadol released after 16 hours, by weight.

Claim 50.(previously presented): The dosage form according to claim 1, which provides a t_{max} from about 3 to about 6 hours.

Claim 51.(previously presented): The dosage form according to claim 1, which provides a W_{50} from about 10 to about 33 hours.

Claims 52-62. (cancelled)

Claim 63. (new): The dosage form according to claim 43. wherein said water insoluble cellulose comprises ethylcellulose.

Claim 64. (new): The dosage form of claim 1, comprising 100 mg tramadol hydrochloride.

Claim 65. (new): The dosage form of claim 1, comprising 200 mg tramadol hydrochloride.

Claim 66. (new): The dosage form of claim 1, comprising 300 mg tramadol hydrochloride.

Claim 67. (new): The dosage form of claim 1, comprising 400 mg tramadol hydrochloride.

Claim 68. (new): The dosage form of claim 1, comprising 600 mg tramadol hydrochloride.

Claim 69. (new): The dosage form of claim 42, comprising 100 mg tramadol hydrochloride.

Claim 70. (new): The dosage form of claim 42, comprising 200 mg tramadol hydrochloride.

Claim 71. (new): The dosage form of claim 42, comprising 300 mg tramadol hydrochloride.

Claim 72. (new): The dosage form of claim 42, comprising 400 mg tramadol hydrochloride.

Claim 73. (new): The dosage form of claim 42, comprising 600 mg tramadol hydrochloride.

Claim 74. (new): The dosage form of claim 43, comprising 100 mg tramadol hydrochloride.

Claim 75. (new): The dosage form of claim 43, comprising 200 mg tramadol hydrochloride.

Claim 76. (new): The dosage form of claim 43, comprising 300 mg tramadol hydrochloride.

Claim 77. (new): The dosage form of claim 43, comprising 400 mg tramadol hydrochloride.

Claim 78. (new): The dosage form of claim 43, comprising 600 mg tramadol hydrochloride.

III. REMARKS/ARGUMENTS

The undersigned gratefully acknowledges the courtesies extended by Examiner Barts during the interview conducted on December 14, 2004.

A. Status of the Claims

Claims 1 and 42-51 and 63-78 are pending. Claims 1 and 42-45 have been amended without prejudice. Claims 52-62 have been cancelled without prejudice. New claims 63-78 have been added. Support for the current amendments can be found in the original specification as filed, e.g., at page 6, lines 6-7 and 18-20 and page 8, lines 17-21. In is respectfully submitted that no new matter has been added by virtue of the present amendment.

The amendments to the claims are made without prejudice to the further prosecution of the pending claims in a continuation application.

B. Statement of Substance of Interview

During the Interview of December 14, 2004, all of the pending claims were discussed and the Applicants maintained their position that the cited prior art does not motivate one skilled in the art to provide a 24 hour tramadol formulation. It was argued that the Examiner's position with respect to the cited prior art is an impermissible "obvious to try" argument.

C. Rejection Under 35 U.S.C. § 103(a)

In the Office Action, the Examiner rejected claims 1 and 42-62 under 35 U.S.C. § 103(a) as being unpatentable over Raffa *et al.* ((Caplus 1992:120745, J. Pharmacol. Exp. Ther. 1992, 260 (1), 275-85)) in view of EP 0147780 to Bondi ("the Bondi reference"). The Examiner's rejection was based on his previous Office Actions dated April 4, 2002, January 14, 2003 and October 21, 2003.

As argued during the Interview, Applicants maintain their position that the claims are patentable over the cited prior art. However, in order to advance the prosecution of the present application, claim 1 has been amended without prejudice to recite as follows:

> *A solid controlled release oral dosage form, comprising,*
> *a therapeutically effective amount of tramadol or a pharmaceutically acceptable salt thereof incorporated into a normal release matrix,*
> *said matrix overcoated with a controlled release coating comprising a polymethacrylate or a water insoluble cellulose,*
> *said dosage form providing a therapeutic effect for at least about 24 hours*
> (Emphasis added)

It is respectfully submitted that the Bondi reference is directed to controlled release dosage forms utilizing polyvinyl alcohol as the controlled release material. The present claims recite a "... controlled release coating comprising a polymethacrylate or a water insoluble cellulose..." which is neither taught nor suggested by the Bondi reference. Therefore, a combination of Raffa et al. with the Bondi reference would not teach or suggest a dosage form comprising a "... controlled release coating comprising a polymethacrylate or a water insoluble cellulose..."

Accordingly, the Examiner is requested to remove the rejection under 35 U.S.C. § 103(a) over Raffa et al. in view of the Bondi reference.

D. CONCLUSION

It is now believed that the above-referenced rejections have been obviated and it is respectfully requested that the rejections be withdrawn. It is believed that all claims are now in condition for allowance.

An early and favorable action on the merits is earnestly solicited. The Examiner is invited to contact the undersigned at the telephone number provided below if he believes that a telephonic interview will advance the prosecution of this application.

Respectfully submitted,
DAVIDSON, DAVIDSON & KAPPEL, LLC

By: _____
Robert J. Paradiso
Reg. No. 41,240

Davidson, Davidson & Kappel, LLC
485 Seventh Avenue, 14th Floor
New York, New York 10018
(212) 736-1940